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THE NATURE OF THE SHIFT OF PLASMA PROTEIN TO THE EXTRAVASCULAR SPACE FOLLOWING THERMAL TRAUMA*†

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DISCUSSION of the circulatory disorder of the burned patient and of the need for fluid to survive is inadequate if it does not include a consideration of the abnormal distribution of the plasma proteins occurring within the body as the direct result of the injury. In the burned, as in the healthy, it is the colloid osmotic pressure exerted by the plasma proteins in differential concentrations on either side of the semi-permeable capillary membrane which apportions water between plasma and interstitial space and maintains blood pressure. It is the sudden increase in permeability of the capillary caused by the burn which destroys the osmotic pressure of the plasma in the area of injury and permits the collection of edema in the wound.

Two misconceptions regarding the distribution of plasma protein are current. First, it is believed that the proteins of plasma circulate only within the blood stream. On the contrary, the normal capillary membrane is incompletely restrictive; albumin, and to a lesser extent globulin, pass out in small concentration from the plasma into the interstitial fluid. The experiments of Drinker on the lymph of dogs, and of others, have made this clear.[1] The lymph protein, and therefore presumably that of the interstitial fluid, varies from less than 1 per cent in the superficial tissues of an extremity to as much as 5.0 per cent in the liver. Though data are limited in the human being to thoracic duct lymph and various edema fluids, it is reasonable to expect that comparable quantities of protein will be found in man outside of the blood vessels. Since

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the protein outside the vessels is still in circulation, eventually reentering the venous blood via the lymph channels, such protein must be taken into account when estimating protein requirements and water distribution in the burned patient.

The second misconception deals with the change in concentration of protein in the plasma following the burn. Because plasma protein has been proved to leak out of the capillary into the wound it has been stated repeatedly that the remaining plasma has a lowered protein concentration. The reverse is true. The lowered protein concentration found some hours after injury is a secondary phenomenon, the result either of withdrawal of water from unburned tissues, or therapy, or of both.

Because an understanding of the redistribution of water and electrolytes is essential in the care of the burned patient, an account is given of the observations, both experimental and clinical, made by the group studying burns at the Massachusetts General Hospital, bearing on the nature of the shift of protein following a burn.

EXPERIMENTAL OBSERVATIONS

The disordered distribution of protein as a result of a burn has been approached experimentally by collecting lymph flowing from the burned foot of the dog. The abnormal flow of lymph engendered by the burn indicates the volume of water passing through the wound, while the discrepancy in protein between the circulating plasma and lymph indicates the permeability of the capillary to protein. The nature of the water and protein leakage from the plasma and the effect of the leakage upon the residual plasma have been examined. Abnormal proteins have also been searched for.

Lymph Flow and Protein Leakage. The experimental method used is that of Drinker. Field, Drinker and White in 1932[2] described an increased flow of water and protein from capillary to lymphatic trunk through an area of sterile inflammation induced by a burn. The foot of a dog was burned by immersion in hot water. The lymph was collected through a cannula placed in a lymphatic trunk above the ankle. Following the injury the protein concentration rose from the normal of 2 Gm./100 cc. to nearly 4 Gm. The flow initially increased by the heat, returned after two and a half hours to that before injury. This classic observation, by measurement of lymph flow and protein concentration, of abnormal capillary filtration in a burn wound of the foot of the dog has been amply confirmed in further work by Drinker and his collaborators,[3] and by ourselves.[4] Evidence of increased flow in the lymphatics in burns has also been obtained by McMaster in smaller animals.[5, 6]

The degree of capillary damage depends to an extent upon the intensity of the burn.[7] A burn of the dog's foot by water at 67 degrees C. for 10 seconds is a threshold burn; it produces a slight, transient increase in lymph flow from that foot and a small but significant rise in concentration of the lymph protein. More intense burns, by hotter water and by longer immersion, are followed by greater flow and protein concentrations; but no matter how severe the burn,

the protein concentration of the lymph is never as high as that of plasma. A cooking burn of boiling water for 20 seconds resulted in a lymph protein concentration of only 5.0 Gm. while the plasma protein was 6.7 Gm. The findings in a typical experiment of the dog's foot with a burn of moderate severity are depicted in Chart 1; the protein concentration of the lymph rose after burning from 1.5 Gm. to 3.5 Gm./100 cc. (See also Table I; compare slight rise in protein concentration of lymph from left foot with that from more severely

TABLE I.—*Distribution of Albumin and Globulin Proteins in Arterial Plasma and Lymph from the Foot of Dogs Before and After Burning.*

Sample		Time Hours	Arterial Pressure mm. Hg.	Hematocrit % Cells	Protein Concentrations Total Gm./100 cc.	Albumin Gm./100 cc.	Globulin Gm./100 cc.	AG Ratio	NPN mg./100 cc.
Experiment No. 1									
Plasma	Pre-burn	..	131	44	5.9	4.4	1.5	3.0	23
	Post-burn	1	144	55	6.4	3.9	2.5	1.6	21
	Post-burn	2	...	62	6.1	3.7	2.4	1.5	22
	Post-burn	3½	143	68	5.9	3.5	2.4	1.5	31
Lymph	Pre-burn	...	...	..	0.9	0.7	0.2	3.5	31
	Post-burn	1	...	..	3.3	2.3	1.0	2.3	28
	Post-burn	3	...	..	4.1	...	...	...	27
	Post-burn	4	...	..	4.4	2.6	1.9	1.4	30
Experiment No. 2									
Plasma	Pre-burn	...	...	34	6.7	3.4	3.3	1.0	45
	Post-burn	4	...	32	6.6	3.4	3.2	1.0	83
Lymph	Pre-burn (Both feet)	...	...	..	2.2	1.1	1.1	1.0	..
	Post-threshold burn (Left foot)	4	...	..	2.7	1.3	1.4	0.9	..
	Post-severe burn...	2	...	..	4.5	2.9	1.6	1.8	..
	Post-severe burn... (Right foot)	4	...	..	4.5	2.6	1.9	1.4	..

burned right foot.) It is thus clear that a portion only of the plasma protein passes with the water through the damaged capillary from blood vessel into the lymphatic; there is an unaccounted for fraction, 1.7 Gm. in the cooking burn described and more in less intense burns.

Where is this unaccounted for fraction of the protein? That it does not lodge in the wound is indicated by the observation that fluids removed by needle from the wound and exuding on the surface of the wound have protein concentrations slightly lower than that of the lymph.[8] There is only one place for it to be and that is still in the blood stream.

Protein Concentration of the Residual Plasma. If the unaccounted for plasma protein remains in the blood stream, dissolved in other plasma water, then the concentration of the protein in the residual circulating plasma must rise, not fall, immediately following the thermal injury. In support of this assumption is the finding of an increased protein concentration of the plasma

of dogs after burning. Plasma protein concentration was followed in 48 dogs burned experimentally (under nembutal anesthesia) and receiving no fluid therapy. In 38 an increase in the protein concentration was observed. In 23 of the 38, only one or two feet were burned and the protein elevation ranged from 0.1 to 1.3 Gm./100 cc., with an average of 0.44 Gm.; in three of these a subsequent dilution was noted, early in one (Experiment 1 of Table I) and late in two. In the other 15 a larger surface of four legs was burned and the protein concentration rose from 0.1 to 4.7 Gm., averaging a 2.09 Gm. rise. Of the 10 remaining animals of the 48, in six, no significant change in concentration was recorded, and in four, falls in concentration of 0.2, 0.3, 0.8 and 1.3 Gm./100 cc. were found. However, the first reading after the burning in each of the 10 animals was delayed, being respectively at the sixth, eighth, 28th and 19th hours in the four whose concentration fell. It is more than likely that a period of increased concentration was overlooked. (Of three dogs maintained under nembutal anesthesia but not burned, two showed a 0.2 Gm. decline and the third a 0.2 Gm. increase in the protein concentration; all three showed a slow rise in hematocrit.)

Osmotic Tension of the Residual Plasma. The increased concentration of protein found in the residual circulating plasma means an increase in the osmotic tension of the plasma which should be accompanied by a withdrawal of fluid from the unburned tissues of the body to the blood stream. The dilution of protein succeeding the initial increased concentration indicates such withdrawal (Experiment 1, Table I).

What evidence is there that the initially more concentrated plasma does not also take back water from the wound? The finding of the slightly lower protein concentration in wound and exudate fluid than in the lymph suggests resorption of water from the edema fluid before it enters the collecting lymphatic trunk. That such resorption by plasma of water in the wound is limited, however, is indicated by the following experiment, using hypertonic purified albumin.* The lymphatic trunks of the hind feet, the neck and the thoracic duct were cannulated; a control flow of lymph was observed. The feet were then burned and when the typical curve of increasing lymph flow from the feet and rising serum protein concentration and hematocrit of the blood were established, the animal was given intravenously 31 Gm. of the albumin in a 25 per cent solution. The hematocrit fell promptly, reaching its lowest level two hours after the injection. This fall in hematocrit represented an enlargement of the plasma volume due to absorption of fluid from the tissues. That this fluid came virtually entirely from the unburned tissues and not from the burn wounds is indicated by cessation of the flow of the lymph from the cervical trunk and a drop in thoracic duct pressure while the increased flow from the feet engendered by the burn continued. There was a slight decrease in flow of the lymph from both feet in the first 20 minutes after the injection

* This experiment was carried out in collaboration with Dr. James T. Heyl. We are indebted to him for his help and to Professor Edwin J. Cohn for furnishing us with the purified bovine albumin used.

followed promptly by a secondary rise to a rate of flow as high as that before the injection. This transitory decline in flow was no greater than that often encountered in control experiments, but because it appeared simultaneously in both feet is believed to indicate a transitory drop in tissue pressure presumably due either to a decrease in rate of capillary filtration into the wound or to an increase in rate of water resorption from the wound area.

The cessation of flow of the lymph from the cervical region persisted for more than three hours in spite of massage and indicated severe dehydration of this unburned region of the body. The contrast between this cessation and the transitory decrease in lymph flow from the wounds suggests that the mechanism for resorption of water locally is also damaged by a burn, the only mechanism for return of fluid from the wound remaining intact being the lymphatic system.

The osmotic influence of the increased concentration of protein found in the circulating plasma (immediately after injury) upon the water concentration of the unburned tissues should depend in part upon its albumin globulin ratio. The lower the ratio the less dehydrating it should be. In the next section the differential permeability of the damaged capillary membrane to albumin and globulin and its effect upon the albumin globulin ratio of the residual plasma is, therefore, considered.

Permeability of Capillary to Albumin and Globulin. Perlmann, Glenn and Kaufman in 1943 examined by electrophoresis the serum and lymph of calves before and after burning.[9] In keeping with the earlier chemical analyses on dogs, as well as on calves, the serum proteins, albumin, alpha, beta and gamma globulins, are to be found in normal lymph; the relative amount of albumin in lymph is higher than in the serum. When first examined, two hours or longer following thermal injury in the calf, the albumin globulin ratio of both serum and lymph had fallen; a greater fall was encountered in the lymph from the burned than unburned leg. Perlmann *et al* concluded that a primary effect of the injury on the capillary wall was "the increased passage of the plasma proteins and a decrease in the differential permeability to albumin."

The permeability of the damaged capillary has been investigated in this laboratory with radioactive diazo dyes and by chemical analysis of the proteins in both the plasma and lymph of dogs. The experiments with the radioactive dyes have been published elsewhere.[4] The dyes, made radioactive by the chemical addition of radioactive bromine, have a rapid and preferential affinity for albumin.[10]* When injected intravenously in less than saturating quantities they bind with the plasma albumin. The rate of their subsequent appearance in lymph is a measure of the rate of passage of albumin across the capillary membrane. Following a severe burn, immersion in boiling water for 60 seconds, the dye concentration in the lymph flowing from the burned foot

* The addition of two bromine atoms to the lipoid soluble portion of the dye molecule apparently decreases water solubility; the colloidal property of the dye and its "fastness" as a dyestuff as well as its biologic properties relative to the protein bond are apparently unchanged.[11]

rose to that in the blood serum within less than an hour. The total protein concentration had risen in the lymph from 2.0 Gm. to only 4.3 Gm./100 cc. while in the serum it started at 7.1 Gm. and gradually rose to 7.7 Gm./100 cc. The conclusion from this experiment was that the capillary wall had become, as the result of the burn, wholly permeable to albumin but not to the globulins.

After a less severe burn, boiling water for only 15 seconds, the dye concentration took longer to rise in the lymph and never reached that of the serum, indicating a still incomplete though increased permeability to albumin.

The chemical analyses** of the plasma and lymph proteins of dogs carried out in this laboratory support the concept of a predominant loss of albumin through the damaged as well as normal capillary membrane. The plasma proteins were examined in 11 experiments. In seven the alubumin-globulin ratio fell, the minimum decrease being from 0.7 to 0.6 and the maximum from 1.5 to 0.6. These seven experiments include the three in which the ratio was measured at two hours or less after injury. Experiment 1 of Table I is one of these three; the pre-burn ratio was unusually high. In two experiments the ratio rose, from 1.0 before burning to 1.6 at the fifth hour and from 2.5 to 3.5 at the 28th hour, respectively, after burning. In the remaining two experiments the ratio did not change, including Experiment 2 of Table I in which the ratio was not measured within the first four hours after burning.

In only four of these 11 experiments was there sufficient lymph for chemical determination of the ratio both before and after burning. In two there was a rise in the ratio. This rise is illustrated in the lymph from the severely burned foot (right) of Experiment 2, Table I, the ratio being greater at two hours than four hours post-burn. There was no significant change in the ratio in this same experiment (Experiment 2, Table I) in the lymph from the lightly burned left foot; the total protein rose only 0.5 Gm. In the other two experiments, there was a fall in the ratio, but in both experiments the initial ratio of plasma and lymph was unusually high (see Experiment 1, Table I).

The fall of the albumin-globulin ratio of the plasma encountered immediately after injury should reduce the rise in osmotic tension indicated by the increase in concentration of the total protein.

Abnormal Proteins. Perlmann, Glenn and Kaufman in their electrophoretic studies in the calf discovered in the lymph from the burned leg a hitherto unseen protein in the range of globulin mobility. They conclude that the substance is a protein released from damaged cells. Our efforts toward identification of abnormal proteins were limited to a study of the activity of certain enzyme systems. Zamecnik[13] has been able to recover in the lymph from the burned feet of dogs specific peptidases of the types associated with intracellular enzyme systems; it is presumed, therefore, that they were released from the cells by the damage.

The amylase and cholinesterase activities of serum and lymph before and after burning have also been examined. The activities found in seven dogs,

** Chemical separation of the plasma and lymph proteins was carried out by the sodium sulfate method of Howe.[12]

both in serum and lymph, were proportional to the total protein concentrations. The slight variations in activity were no greater than those encountered in control animals. The variations usually, but not always, paralleled alterations in the protein concentration. These findings are interpreted to mean that there is no specific effect of burn trauma either upon the activity of the two enzyme systems as they relate to the extracellular fluid (plasma and interstitial fluid), or upon the permeability of the capillary membrane creating a predilection for their passage.

The fibrinogen level* of blood and lymph was followed in four dogs before and after burning. The normal level of fibrinogen in the lymph was less than half that in the plasma. Following burning the level in both plasma and lymph rose, slightly in the plasma, more in the lymph until that of the lymph was approximately that of the plasma. (There was thus no evidence obtained in these few experiments of retention of fibrin in the wound.)

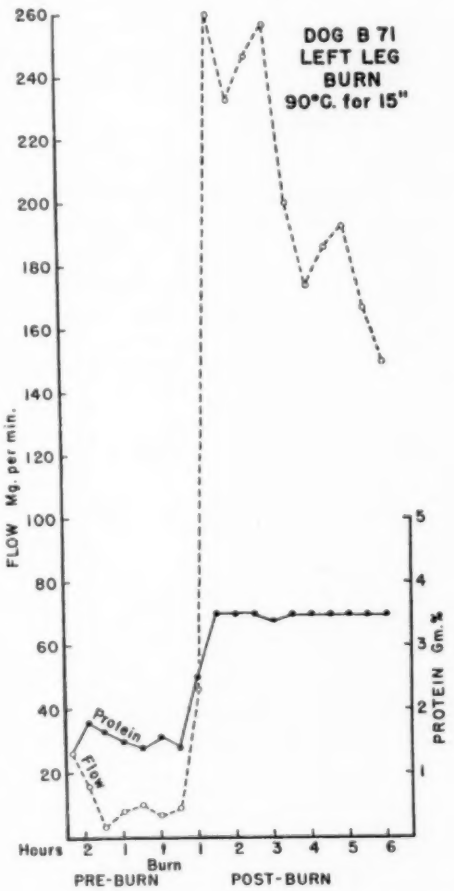

CHART I.—The increase in flow and protein concentration of lymph from the foot of a dog following burning. The flow of lymph before burning was obtained only with massage; following the burn there was a spontaneous flow the rate of which rose precipitously in the first hour and a half. In the same period the protein concentration more than doubled. After maximum edema had been reached the flow gradually decreased but the protein concentration remained at the same elevated level.

CLINICAL OBSERVATIONS

It has not been feasible to examine the lymph of burned patients; analysis of the changes in capillary permeability and the shift of protein to the wound, therefore, must depend upon a comparison of blood plasma and the fluid removed from the blebs of the wound.

The chemical and electrophoretic studies of plasma and bleb fluid carried out on this series of burned patients confirm those on animals. As the plasma circulating through the wound area loses water into the wound, a portion of the proteins dissolved in that water is retained within the vascular tree, and there is conse-

* Fibrinogen of plasma and lymph was measured by the method of Cullen and Van Slyke.[14] The normal plasma level is from 0.3 to 0.6 Gm./100 cc.

quently an initial rise in plasma protein concentration and in osmotic power.

Contrast of Plasma and Bleb Fluid Proteins. The literature records several measurements of the protein withdrawn from the blebs of burned patients;[15, 16] the concentrations recorded are 60 to 80 per cent of that expected of the plasma. The interval between injury and withdrawal of the fluid and a simultaneous plasma protein measurement are usually not also recorded.

The total protein concentration of the fluid of a number of unruptured blebs was examined at varying intervals following injury. The fluid was withdrawn, without breaking the bleb, by sterile needle and syringe inserted at the side or base of the bleb. A few of the patients afforded a sufficient number of blebs for repeated taps. A fluid was discarded if the gross appearance of the wound suggested infection or if the fluid was cloudy on withdrawal. Most of the fluids

TABLE II.—*Concentrations of Plasma and Bleb Fluid Proteins of Burned Patients at Varying Intervals Following Burning.*

		Bleb Fluid Proteins				
Case No.	Time Post-Burn	Total Gm./100 cc.	Albumin Gm./100 cc.	Globulin Gm./100 cc.	AG Ratio	Plasma Protein Gm./100 cc.
116	2 hrs.	4.2	See Table III		1.71	7.2
63	2 hrs.	4.6				
58	3 hrs.	5.1	3.9	1.2	3.2	
114	36 hr .	3.1	...	...	...	5.7
120	51 hrs.	4.3				
120	54 hrs.	4.7	...	...	...	6.5
81	3 days	4.4	2.8	1.6	1.8	
80	5 days	4.9	2.9	2.0	1.5	
119	5 days	3.6	...	...	...	6.6
119	5 days	3.2	...	...	...	6.5
119	6 days	4.0	...	...	...	6.5
28	5 days	3.6	2.1	1.5	1.4	6.1
28	6 days	3.3	...	...	...	5.9
28	12 days	2.5				
17	6 days	2.2	...	...	...	8.1
38	7 days	1.5	...	...	...	5.4
19	7 days	1.8	...	...	...	7.0

were cultured to insure exclusion if bacterial inflammation were present. The concentration of the plasma was measured simultaneously in most instances. The rate of passage of sulfadiazine from blood stream to bleb fluid was measured in three patients at intervals after injury (2, 60 and 100 hours) in order to ascertain whether the intimacy of bleb fluid and blood plasma persisted.

The total protein concentration of the fluid removed from a bleb of a burn wound was found to be always lower than that of the patient's circulating blood plasma. The chemical analyses from representative patients with partial thickness burns are given in Table II. The analysis of the electrophoretic pattern of the fluid and plasma of one of two patients, generously examined for us by Dr. G. E. Perlmann, is given in Table III. The protein concentrations of bleb fluid and plasma of patients correspond closely to those of the lymph from the burned foot and plasma of dogs. The highest concentrations

in the bleb fluid are found within the first days following the burn. The fluids withdrawn after the fifth day show concentrations decreasing with time, suggesting not only resorption or breakdown of proteins as healing progresses, but also that the protein concentration of the normal interstitial fluid is considerably lower than that of the wound edema fluid, and at least as low as that of the normal peripheral lymph of the dog.

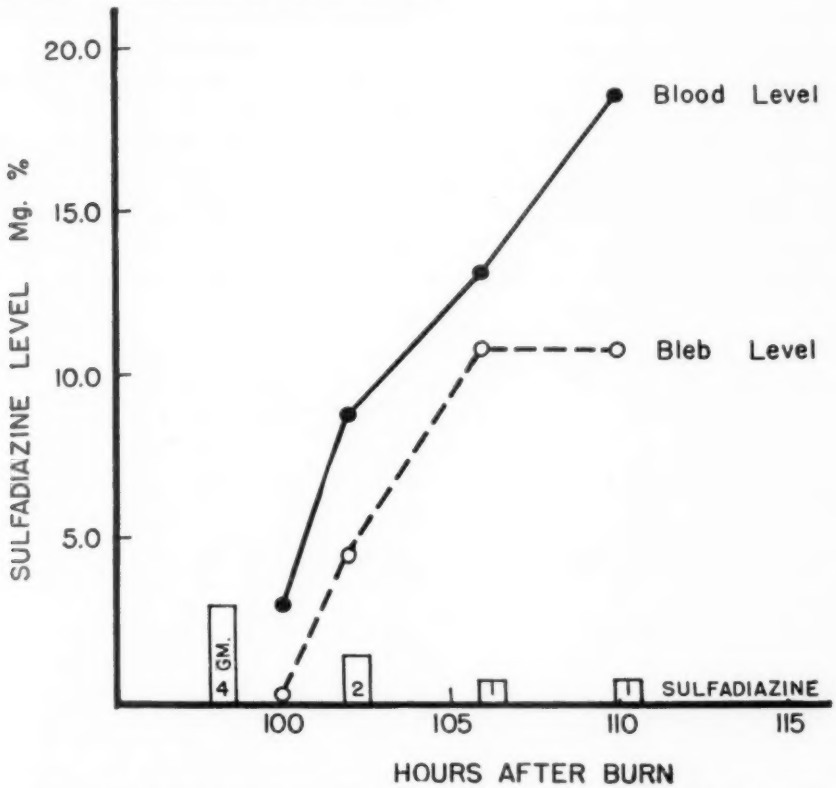

CHART II.—Case 119. Concentration of sulfadiazine in blood and bleb fluid after withholding the drug until the fourth day. The patient had a partial thickness skin burn with multiple blebs. Four grams of sulfadiazine were given by mouth 98 hours after the burn. The rise in concentration in the bleb fluid is almost as prompt as in the blood stream indicating rapid exchange through the wound even at this late time after the burn. (Reprinted with the permission of The Journal of the American Medical Association.)

The albumin-globulin ratio of bleb fluid is high, higher than that of the plasma in the first hours after injury (see Table II, Case 58, and Table III). The observations made after 36 hours show it to be in the range of that of normal plasma. Too few observations have been made to tell when the ratios of plasma and bleb fluid approach each other. The ratio of the one bleb fluid observed at 36 hours was still increased as compared with that of the plasma, but the plasma had an abnormally low ratio and total protein concentration, perhaps related to the patient's preexisting, diffuse osteoporotic disease of the bones of unknown etiology.

The results of the study of the passage of sulfadiazine from plasma to bleb fluid have already been reported[17, 18] but a resumé is given here to emphasize the rapidity with which the plasma and the fluid of the non-infected burn bleb communicate with each other, even as long as five days after injury. To a patient with several blebs suitable for multiple tappings, sulfadiazine was given by mouth at the ninety-eighth hour after burning (Chart II). The level of sulfadiazine was observed in both plasma and bleb fluid by analysis of samples of each fluid taken at the second, fourth, eighth and twelfth hours after the first dose of sulfadiazine. The rise in the level of sulfadiazine in the bleb fluid was found to lag only slightly behind that in the plasma.

These observations in burned patients point to an increased but incomplete permeability to protein of the capillary membrane damaged by a burn, as in the dog. There is apparently a greater permeability to albumin immediately following injury. That the findings in the bleb fluid are not due to a stagnant puddling of the fluid is suggested by the promptness of the passage of the sulfadiazine from the plasma into the bleb.

TABLE III.—*Electrophoretic Observations on Blood Serum and Bleb Fluid of Case 116. (Electrophoresis carried out in Na-diethylbarbiturate buffer of pH 8.6 and ionic strength 0.1)*

			Concentrations in Percent of Total Protein				
				Globulin			
Time Post-Burn	Protein Gm./100 cc.	AG Ratio	Albumin	Alpha-1	Alpha-2	Beta	Gamma
Serum No. 1—2 hours....	7.2	1.00	50.0	7.9	6.4	18.9	16.5
Serum No. 2—6 hours....	5.5	.85	45.9	10.1	11.3	17.8	14.9
Bleb fluid—2 hours.....	4.2	1.71	63.1	7.4	3.7	12.3	13.5

Protein Concentration of Residual Plasma. If one can assume that bleb fluid is essentially burn wound fluid, the filtrate from the damaged capillaries, the finding that the bleb fluid protein concentration is lower than that of the plasma, indicates that only a part of the plasma protein escapes with the plasma water from the capillary into the wound.* In the patient as in the experimental

* In the burn wound both of the human being and of the dog there are doubtless gradations of capillary damage and of increased permeability of the capillary membrane. The capillaries nearest the surface must receive the maximum trauma and their membranes may be rendered so permeable that circulation ceases within them, the lumen becoming plugged with cells. Those deepest in the wound must receive minimal damage and, as judged by the experimental observations,[7] allow to seep out a fluid only slightly increased in volume and with a protein concentration only slightly higher than normal. From the capillaries between these extremes, the volume and the protein concentration of the filtrate presumably varies with the depth of the capillary. Thus the wound fluid, or the lymph flowing from a wound, should be a mixture of capillary filtrates. Whether or not the fluid is a mixture is an academic question; the concentration of protein remaining in the vascular tree will depend upon the final concentration in the entire wound area and the total volume of fluid seeping into the wound rather than upon the concentration of the filtrate from any one capillary.

animal, therefore, an increase in concentration of the protein in the residual circulating plasma is to be expected in the first hours after injury. It is of course not possible to obtain in the burned patient the necessary control blood sample to test this assumption, for the patient arrives in the hospital already burned. Based on two sets of observations, we have the impression, however, that such is the case.

The protein concentration of the plasma within the first three hours after injury and before the onset of therapy in 19 extensively burned patients in whom this measurement was obtained, was 7.0 Gm./100 cc., the range being from 6.3 to 7.7 Gm. The lowest level encountered was in the plasma of a six-year-old boy who had long been a feeding problem and was undernourished; also included are another previously ill patient and three chronic alcoholics, all of whose levels were among the lowest found. The average of the highest protein concentration observed within the first 12 hours after injury and after onset of therapy in 46 patients with either extensive burns or circumscribed

TABLE IV.—*Plasma Protein Concentration of Two Extensively Burned Patients in the Initial Hours after Injury.*

Case No.	Extent of Burns	Hours After Burning	Plasma Protein Gm./100 cc.	Hematocrit % Cells
217	78%	0.8	6.9	50
		1.5	6.5	43
		5.5	6.9	50
		8.0	8.0	51
		11.0	7.3	48
		17.0	6.0	39
		20.0	5.4	42
254	45%	1.3	7.7	50
		3.5	8.0	50
		4.5	7.1	47
		8.0	7.4	46
		11.0	7.4	47
		14.5	6.4	43

skin burns and pulmonary damage, was 7.5 Gm./100 cc., with a range of 6.3 to 9.5 Gm. These averages and ranges are above those generally accepted as normal. Phillips, Van Slyke *et al*[19] give a range of 6.0 to 7.3 Gm./100 cc. Our own observations agree with this range for normal adult human beings.

The reinforcement of the concept that the initial change in plasma protein level is toward an increasing concentration was encountered in burned patients whose therapy was either delayed or adjudged inadequate in the first few hours after entry to the hospital. The findings in two patients (Cases 217 and 254) illustrating this event are given in Table IV. During the period of inadequate treatment there was either no change or a rise in the total protein concentration of the plasma. Inadequacy of therapy in these patients was judged by the failure of the hematocrit to fall promptly toward normal, or

because it rose further, or because the urinary output was meager. In contrast, the extensively burned patients receiving therapy adequate for rehydration as judged by a falling hematocrit and renal output of 30 cc. or more per hour, were found to show a decrease in plasma protein concentration.

COMMENT

Survival of the burned patient depends upon the maintenance of a physiologic environment for the cells of the unburned organs. Excessive dehydration or hydration can conceivably result in irreversible injury. From examining the shift in protein from capillary to wound, the character of the residual protein in the plasma has been determined; it is this protein which controls the osmotic balance between plasma and the interstitial fluids caring for the nutrition of the unburned cells. Its initial increase in concentration in the absence of therapy means that the unburned tissues are being dehydrated.

Two qualifications are indicated in interpreting the observations recorded in this paper. The osmotic tension of the residual circulating plasma is presumably not as high as suggested by the total protein concentration; the decrease in the albumin-globulin ratio tends to cancel the rise in osmotic power. No measurements of the osmotic tension were carried out.

The second qualification is in regard to the origin of the decrease in the albumin-globulin ratio in the plasma. In addition to the preferential loss of albumin through the damaged capillary into the wound, new globulin may be added to the circulating plasma. White and Dougherty[20] have described in experimental animals a disintegration of lymphocytes with release into the circulation of globulin protein as a result of the administration of either adrenotropic or adrenocortical extracts. Selye has found adrenotropic and adrenocortical hyperactivity to be an expected sequel of trauma.[21] The relation of the lymphocyte-protein release to the endocrine system in the human being following burn trauma is discussed in a subsequent paper.[22] But it remains to be discovered to what extent in the burned patient such a reaction to trauma contributes to the change in albumin-globulin ratio of the plasma of the burned patient. It obviously cannot account for the entire fall of the ratio in the plasma; in such case the ratio in the lymph of the burned dogs and in the bleb fluid of the patients would be identical with that of the plasma.

The seeming difference between the observations of Perlmann, Glenn and Kaufman in the burned calf and ours in the burned dog and human being is probably one of interpretation, not of fact. It is possible that had Perlmann et al measured samples of lymph within the first two hours after injury, results comparable to ours in the same period would have been found.

The interest of Perlmann and her colleagues was centered on the search for abnormal proteins, the result of burn damage; a hitherto unidentified protein in the range of globulin mobility was disclosed by electrophoresis in the burned calf. Doctor Perlmann was unable to find by electrophoresis a comparable protein in the bleb fluid or plasma of the two patients of this series examined by her. In examining the bleb fluid of nine of the burned and one

frostbitten patient, Doctor Zamecnik found 11-fold differences in peptidase activity indicating the occasional release of such intracellular enzymes in the wounds of human beings as well as in dogs. Our search for other abnormal proteins in burned patients by measurement of cholinesterase and amylase activity of bleb fluid and plasma proved negative.

CONCLUSIONS AND SUMMARY

The nature of the shift of protein from the vascular bed into the burn wound has been examined experimentally and in the burned patient. In the dog the flow of protein through the wound has been measured by collecting lymph and in the patient by comparison of plasma and bleb fluid. Comparable results with the same implications have been found in the dog and the human being.

Proteins and fluid are in continuous slow circulation through the burn wound, returning to the blood stream via the lymphatics. The free flow in the lymphatics apparently accounts for the rapid resorption of edema in the uninfected burn wound after 48 hours;[23] as the capillary membrane heals, resorption is more rapid than the filtration from capillary into wound.

The total protein concentration of fluid in the burn wound is always lower than that of the plasma; more water than protein is lost from capillary into wound. The initial change in the residual circulating plasma is therefore an increase in concentration of total protein. This more concentrated plasma presumably exerts an increased colloid osmotic pressure in the unburned regions of the body. Following resorption of water from unburned tissues and fluid therapy, this increased concentration of the proteins of the residual plasma is replaced by a dilution.

The initial increase in protein concentration and osmotic power of the circulating plasma is not encountered following a hemorrhage of whole blood where the entire plasma is lost.[24] For a given loss of water from the vascular bed, that is for an equal reduction in blood volume, the undamaged tissues of the burned patient face a more rapid dehydration than those of the patient following a hemorrhage.

In addition to differences in total protein concentration, there are also differences in the albumin-globulin ratio of wound fluid and plasma. These differences depend upon differential capillary permeability; a greater than normal proportion of albumin passes the damaged membrane. The wound fluid thus has a higher ratio than plasma and the plasma ratio falls initially. This fall in ratio of the plasma presumably tempers the rise in osmotic power indicated by the increase in total protein concentration.

In a search for abnormal protein as a result of the injury, enzyme systems have been investigated in both plasma and lymph. An increase in activity was found of a peptidase of intracellular type in dog lymph following burning with divergent activities in bleb fluid of the human being.[13] The amylase and cholinesterase systems of blood and lymph of the dog were also studied before

and after burning. Neither evidence of disturbance of these enzyme systems nor of preferential passage of these proteins through the damaged capillary membrane was found.

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TRAUMATIC CHYLOTHORAX*†

A REVIEW OF THE LITERATURE AND REPORT OF A CASE TREATED BY LIGATION OF THE THORACIC DUCT AND CISTERNA CHYLI

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INTRODUCTION

TRAUMATIC CHYLOTHORAX, according to Zesas,[77] was first described by Longelot in 1663. It is a rare condition with a grave prognosis. In 1938 Shackelford and Fisher[65] reviewed the literature, discarded 11 incomplete cases, summarized 39 remaining, and added two of their own. In 1947 Lampson[40] summarized 17 subsequent reports and added one of his own, making a grand total of 59 which have been recorded. Olsen and Wilson[53] were able to find only nine cases of chylothorax from any cause in the records of the Mayo Clinic, but since seven of these nine were discovered between December, 1942, and November, 1943, they concluded that chylothorax is more frequent than a review of the literature might indicate, and that the diagnosis is frequently not made. On the other hand, Elliott and Henry[24] found only two cases out of a total of 600 samples of hemothorax fluid examined, covering an "experience of far more than a thousand chest wounds." The relative infrequency of chylothorax in war wounds is explained on the basis of the close proximity of the thoracic duct to vital structures, injury of the one implying fatal damage to the others.

EMBRYOLOGY AND ANATOMY

Lymphatics arise independently of blood vessels from discrete mesenchymal spaces which become lined by endothelial cells. The adult lymph system is derived by a process of fusion and budding of these anlagen. Lymph sacs develop with openings into veins. Two of these, the right and left jugular, persist and become the openings of the right lymphatic duct and the thoracic duct, respectively, into the great veins of the neck. Another lymph sac, lying anterior to the body of the second lumbar vertebra, becomes the cisterna chyli. The embryonic thoracic ducts are bilateral and have numerous cross anastomoses. Persistence of these real or potential cross anastomoses becomes an important factor in the development of collateral lymph circulation following injury to or obstruction of the duct.[41]

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The anatomy of the thoracic duct has been investigated by numerous authors.[10, 17, 55, 61, 69] The duct varies from four to six millimeters in diameter. Its walls are composed of smooth muscle and fibrous tissue.[1] It has its origin from an irregular triangular sac-like dilatation, the cisterna chyli, which is situated on the anterior surface of the body of the second lumbar vertebra, to the right side of and behind the aorta, by the side of the right crus of the diaphragm. Tributary trunks, the bilateral lumbar and the intestinal, enter the cisterna from below. Immediately cephalad, at the commencement of the thoracic duct, on either side, is a descending trunk draining the lymph from the lower six or seven intercostal spaces.[32] Entering the thorax through the aortic hiatus of the diaphragm, the duct ascends between the azygos vein and the aorta to the fifth thoracic vertebra, where it inclines toward the left, enters the superior mediastinal cavity, and ascends behind the arch of the aorta and the left subclavian artery, and between the left side of the esophagus and the left pleura, to the upper orifice of the thorax. Passing into the neck the duct forms an arch which rises to a variable extent (as much as five and one-half centimeters)[39] above the clavicle. It then crosses anterior to the subclavian artery, the vertebral artery and vein, and the thyrocervical trunk or its branches, and empties into the vascular system at the angle of junction between the left subclavian and left internal jugular veins.

The right thoracic duct is about 1.25 centimeters long, and normally ends in the right subclavian vein at its junction with the right internal jugular. This duct and its tributaries drain the right side of the head and neck, the right upper extremity, the right side of the thorax, right lung, right side of the heart, and part of the convex surface of the liver.

Lymph from the remainder of the body, and intestinal chyle, pass into the venous system by way of the main thoracic duct.

The lower thoracic duct and cisterna chyli represent the "hub" or central collecting point of the chyle and the major portion of the lymph from the entire body.

The usual textbook description of the thoracic duct, as above portrayed, does not take into account the extreme variability, based on differences in embryonic development, which may occur.

Davis[17] described nine types, ranging from the complete persistence of bilaterally symmetrical ducts to the persistence of one single trunk. Stuart[69] summarized the anatomic variations of the thoracic duct and said that the usual description as a single channel throughout its course "may almost be regarded as a description of an abnormality, so frequently is it found to branch and subdivide." He mentioned cross anastomoses between double branching ducts within the thorax and called them "surgically unimportant"!

Brinton[10] described the various ways in which the thoracic duct empties into the veins of the neck. He stated that at the mouth of the duct in the wall of the vein there are two valves which prevent backflow of blood into the lymph channel. Sometimes it empties into the right side, and sometimes there are several openings into the vein, producing a delta-like arrangement.

Parsons and Sargent[55] showed that the duct has two terminal branches in 18 out of 40 cases.

Dissections at the Rhode Island Hospital, carried out by Dr. Charles Begg (Fig. 4), have emphasized the important relationship of the thoracic duct to the sympathetic nervous system. It is not generally recognized that low in the right chest the duct may lie directly against the azygos vein and that the great splanchnic nerve may lie directly over the vein. These relationships vary. Frequently the splanchnic nerve is within a few millimeters of the thoracic duct at this level.

Variations in position of the sympathetic nervous system likewise occur and in those subjects where the great splanchnic nerve enters the abdomen through the aortic hiatus[57] the thoracic duct and splanchnic nerves are of necessity very closely related.

Because of its many variations in position and its close proximity to the esophagus, pericardium, pleura, great vessels and sympathetic nerves, surgical injury of the thoracic duct has become an increasingly important hazard as modern surgery invades the deeper structures of the neck, chest and upper abdomen. Harvey Cushing's statement[15] is no longer true that the main part of the duct lies in a surgically forbidden region of the body and that "in the neck alone, and there only, under unusual circumstances is it accessible."

PHYSIOLOGY

The function of the thoracic duct is the conveyance of chyle and lymph into the general circulation. Chyle flows at the rate of .38–3.9 cubic centimeters per minute[14] or at the rate of 60–190 cubic centimeters per hour.[42] With complete severance of the duct it is therefore theoretically possible to lose over four liters within a 24-hour period. Pressure within the duct is normally low, but after ligation may be as high as 35 centimeters of water.[23] Flow of chyle is favored by the slightly higher pressure in the duct than in the veins and by respiratory motion with its fluctuating changes of intrathoracic pressure. Intestinal peristalsis, muscular activity, and coughing or straining increase the intraductal pressure. Beck[5] suggested that the pulsations of adjacent arteries may be an important factor in producing lymph pressure.

CHYLE

The composition of chyle is unique and characteristic[30] and has been described by many authors.[20, 30, 44, 47, 51, 72]

The chief characteristics of chylous fluid[37] are:

1. Milky appearance.
2. Generally shows distinct creamy layer on standing.
3. Finely emulsified, with fine fat globules.
4. No odor or odor corresponding to that of food eaten.
5. Alkaline reaction.
6. Specific gravity generally exceeds 1.012.
7. Degree of opalescence more or less constant.
8. Sterile and resists putrefaction.

9. Fat content generally high, 0.4 to 4 per cent, and like fat in food.
10. Total solids usually greater than 4 per cent.
11. Total protein generally exceeds 3 Gm. per 100 cubic centimeters.
12. Salts and organic substances approximate the values found for chyle from the thoracic duct.

The chemical analysis of chyle and lymph in man (Munk), quoted by Lewin[44] is as follows:

	Chyle	*Lymph*
Water	92.2 per cent	95.2 per cent
Solid	7.8 per cent	4.8 per cent
Fibrin	0.1 per cent	1.0 per cent
Proteins	3.2 per cent	3.5 per cent
Fats, licithin and cholesterin	3.3 per cent	traces
Extractives	0.4 per cent	0.4 per cent
Salt	0.8 per cent	0.8 per cent

Sixty to 70 per cent of ingested fat is conveyed to the blood stream by way of the thoracic duct.[7] The fat content of chyle varies with the diet.[62]

The protein content of chyle is less dependent on diet and varies from one to six Gm. per 100 cc.[22] It is usually above three Gm. per 100 cc.

Lampson[40] has demonstrated that chyle is bacteriostatic against cultures of Escherichia coli and *staphylococcus aureus*. His work explains the fact that chyle resists putrefaction. Empyema is rarely mentioned as a complication of chylothorax in the literature.

Chyle is an important vehicle for the mobilization of proteins. In the presence of hemorrhage, protein is redistributed via the thoracic duct and made available for essential functions.[13]

Any description of chylous fluid is incomplete without mention of the fact that it is rich in lymphocytes. Injuries to, or obstruction of the thoracic duct are known to be associated with diminution or disappearance of lymphocytes and eosinophiles from the circulating blood.[6, 22, 51, 60, 66, 75] Davis and Carlson[16] state that "normally the lymphocytes enter the blood with the lymph stream, and not by direct migration through the capillary walls from their place of formation. They are as much a part of the lymph as the erythrocytes and leucocytes are of the blood. Red blood cells are not to be regarded as normal constituents of the lymph."

A progressive fall in lymphocyte percentages in the blood is one of the clinical manifestations of chylothorax.

We have been unable to find any explanation for the reported reduction or disappearance of eosinophiles.

ETIOLOGY OF CHYLOTHORAX

The causes of traumatic chylothorax as described by Shackelford and Fisher[65] and Lampson[40] are shown in Table I.

It is possible that these summaries may not include all reported cases of traumatic chylothorax when it is remembered that so-called spontaneous

cases, especially in infants,[9] may actually have been produced by hyperextension of the spine during delivery, or too vigorous manual attempts at resuscitation[25] or coughing and vigorous crying.

It is interesting to note that no cases of surgical trauma of the thoracic duct were mentioned in Shackelford and Fisher's report and that four cases of surgical intrathoracic injury of the thoracic duct resulting in chylothorax have

TABLE I

	Shackelford and Fisher (1938)	Lampson (1947)
Crushing injuries	17	1
Wounds (bullet and stab)	8	5
Fall from height	6	2
Blow on chest	5	2
Thrown against seat of auto	4	..
Hyperextension	1	..
Auto accident with collision	..	2
Hit by auto	..	1
Severe coughing	..	1
Surgical accident	..	4
	41	18

been reported since 1938. These resulted from lysis of adhesions of the left lung by thoracoscope,[21] resection of a Ewing's tumor of the right tenth rib and vertebra,[66] and from injury to the duct during sympathetic denervations.[56, 75] The first two survived; the last two died.

In Whitcomb and Scoville's case injury to the duct was recognized at the time of sympathectomy and the duct was doubly occluded, above and below, with silver clips. The patient nevertheless developed chylothorax and subsequently succumbed during the intravenous administration of chyle. It occurs to us that metal clips are not the safest agents available for the ligation of such a delicate structure as the thoracic duct.

Peet and Campbell's case likewise occurred as a complication of sympathectomy and succumbed suddenly following surgical ligation and the intravenous administration of chyle.

Although only four cases of accidental intrathoracic surgical injury of the thoracic duct resulting in chylothorax have been reported, such injuries are not as rare as might be supposed.

We know of one recent case of traumatic chylothorax following sympathectomy[67] and another as a result of erosion of the thoracic duct from a catheter placed in the chest for drainage of an empyema.[12] Several cases have been observed following resections of the esophagus[12, 70] for tumors of that organ.

Occasional injury of the thoracic duct is inevitable, even in the most experienced hands, during extensive intrathoracic procedures, especially esophagectomy and sympathectomy. Indeed, the adequate removal of certain tumors of the esophagus may require deliberate section of the duct. Smith-

wick[67] estimates that he has injured the thoracic duct 15 or 20 times in his extensive experience with thoracolumbar sympathectomy. Chylothorax developed in only one case, where injury of the duct at the time of operation was not recognized and adequately treated.

The importance of recognition and immediate appropriate treatment of accidental surgical injuries of the duct in the prevention of chylothorax cannot be overemphasized.

PATHOLOGY

There is considerable discussion in the literature as to the actual mechanism of the development of chylothorax following injury to the thoracic duct, since anatomically the duct is extra-pleural in position, and since chylothorax, by definition, is an accumulation of chyle within the pleural cavity. Watts[74] quoted Hammesfahr to the effect that chyle escapes into the pleural cavity through the normal intercellular spaces between the endothelial cells, but Lillie and Fox[45] quoted J. L. Yates to the effect that there are no intercellular spaces in this region, and a perforation of the pleura is always present though frequently not recognized.

Blalock, Cunningham and Robinson[6] state that in their experimental animals "chyle entered the pleural cavity through an uninjured pleural layer."

Retropleural accumulations of chyle have been reported,[11, 47, 51] and it is probable that the usual delay which occurs between injury and the development of chylothorax represents the time required for erosion of the contiguous pleura and perforation of an enlarging chyloma into the pleural cavity.[53, 65]

DIAGNOSIS

Traumatic chylothorax is more common on the right than on the left except in the case of penetrating injuries, where it is more common on the left.[47, 74] As a general rule, injuries low in the thorax result in right chylothorax and high injuries in left.[65]

The signs and symptoms are what might be expected upon the rapid accumulation of chyle within the pleural cavity. The immediate effects are mechanical in nature, resulting from compression of the lung, reduction in vital capacity and perhaps a shift of the mediastinum, with angulation of the great blood vessels.[65, 68] They are as follows:

1. Delay in onset, two days to six and one-half years[4] following injury. The usual period of delay is two to ten days.[75]
2. Dyspnea—of sudden onset.
3. Shock, with elevated thready pulse, low blood pressure, pallor, cold clammy skin, and subnormal temperature.
4. Rapid and complete relief of symptoms following thoracentesis.
5. Reaccumulation of fluid and recurrence of symptoms, depending upon the quantitative escape of chyle into the pleural cavity.

The rapidity of onset and severity of symptoms, and the equally rapid relief following thoracentesis are characteristic and distinguish the condition from shock due to hemorrhage or other cause. Because of the pinkish gray

purulent appearance of the fluid, the unwary observer may be led into the mistaken diagnosis of empyema,[19, 24, 74] or hemothorax.[45]

The secondary symptoms and frequent lethal termination of chylothorax result from persistent loss of fluid, fat, protein and lymphocytes in cases where healing does not take place spontaneously or where successful surgery is not accomplished. In other words, the patient "bleeds" to death, his death being due to loss of lymph and chyle, rather than to loss of actual blood.

These signs and symptoms may be listed as follows:

1. Gradual or rapid loss of weight.
2. Dehydration.
3. Reduction in serum protein, mirroring a more significant loss of total body protein.
4. Reduction in blood and tissue fat.
5. Disappearance of lymphocytes and eosinophiles from the circulating blood.
6. Inanition, oliguria, thirst.
7. Death.

The patient may live for weeks or months, or die in a few days, depending upon the extent of the injury to the duct, complications of the original trauma, and the type and effectiveness of the treatment instituted.

Chylopericardium[76] and chylous ascites[36, 46] may occur in association with chylothorax. These are unusual and rare complications.

The diagnosis of chylothorax is not difficult. The clinical characteristics as described might conceivably be confused on rare occasions, but aspiration and laboratory identification of the intrapleural chyle gives conclusive evidence.

MORTALITY

Mortality rates for chylothorax approximate 50 per cent. In Mouchet's[50] 43 cases, the death rate was 41 per cent. McNab and Scarlett[47] reported 53 per cent and Lampson[40] 45 per cent out of a total of 58 cases analyzed.

TREATMENT

There is one universally stated and generally accepted maxim concerning the treatment of chylothorax to be found in the literature, and that is, "Do not operate." As has already been mentioned, Harvey Cushing described the intrathoracic duct as lying in surgically forbidden territory. In a personal communication to Lillie and Fox[45] in 1934, J. L. Yates said, "Ligation in the chest is almost certainly fatal." Florer and Ochsner[27] say, "Direct surgery to repair the duct has been completely unsuccessful, resulting in 100 per cent mortality." Following a practice attempt at ligation below the diaphragm in a cadaver Shackelford and Fisher[65] say, "Surgical ligation of the duct is physiologically compatible with life, but clinically impractical at present." The preponderance of opinion against direct attack upon the ruptured intrathoracic duct is almost overwhelming.[3, 24, 25, 31, 66, 68, 74, 75]

The accepted treatment of chylothorax has as its aim (1) Reduction of the volume of chyle and the prevention of respiratory and vascular collapse

from intrapleural pressure; (2) Maintenance of nutrition, and (3) Measures designed to favor healing of the injured duct. A summary of these various procedures follows:

1. Prevention of the mechanical effects of chylothorax.
   a. Limitation of fluid intake.
   b. Low fat diet.
   c. Avoidance of lymphagogues, especially intravenously.[5]
   d. Repeated thoracentesis.
2. Maintenance of nutrition.
   a. High carbohydrate, high protein diet.
   b. Maintenance of fluid balance.
   c. Transfusions of blood, plasma, and blood substitutes.
   d. Feeding of chyle by mouth.[36]
   e. Feeding of chyle by rectum.[34]
   f. Intravenous administration of chyle.[3, 46, 52]
   g. Intrasternal administration of chyle.[56]
3. Measures to promote healing.
   a. Phrenicotomy or phrenic neurotripsy.[27, 51, 64]
   b. Pneumothorax.
   c. Phrenicolysis and pneumoperitoneum.[27]
   d. Retropleural drainage.[11, 47, 63]
   e. Thoracotomy or thoracoplasty.[58, 77]
   f. Injections of sterile broth.[59, 64]
   g. Injections of Gomenol in oil.[49]
   h. Intrapleural irrigations with azochloramid.[31]
   i. Roentgen-ray therapy.[53, 71]
   j. Surgical ligation.

One need only remember the mortality statistics of chylothorax to realize that the above measures are not eminently successful. Repeated thoracentesis and the maintenance of nutrition are certainly essential, but the latter is most difficult to achieve. In the last analysis, cure of the condition depends upon the establishment of collateral lymph circulation and/or the closure of the injured duct.

In cases of frank laceration of the thoracic duct, it is impossible to maintain normal fluid, fat, and protein reserves by dietary methods.[46] In spite of high protein diet, values for serum protein progressively decline. Limitations of fluid intake and dietary fat do not reduce the volume of chyle.[62] The progressive loss of protein is more important than is the loss of fat.[48]

Parenteral introduction of chyle, first recommended by Oeken,[52] has apparently been of benefit in some cases,[3, 28, 64, 66] but has not reduced the over-all mortality of 50 per cent.[75] This treatment is hazardous. Blalock and coworkers[46] reported the extension of a preexisting thrombophlebitis in their case following the administration of aspirated chyle. Schnug and Ransohoff[64] reported a marked phlebothrombosis which made intravenous administration difficult. In 1938 Johnson and Freeman[38] presented evidence that there is some hemolytic agent in chyle and in 1940 they[29] stated that only thoracic duct lymph has this property, other lymph not being hemolytic. In 1942 Whitcomb

and Scoville[75] reported a sudden death during the intravenous administration of chyle. They attributed the death to anaphylaxis. Other cases of sudden death following this treatment have been recorded.[56]

Phrenic neurotripsy, as recommended by Nowak and Barton,[51] is an ingenious suggestion, the object being to favor healing in low injuries of the duct. Healing in their case was "presumably due to elongation and narrowing of the crural sulcus with apposition of the diaphragmatic and mediastinal parietal pleurae." Other mechanisms suggested were reduction of the aspirating action of respiratory movements on the open duct and increased tendency for clot formation due to limitation of respiratory movements. The value of this treatment would depend in part upon the location of the lesion. It has been employed with doubtful results by several authors.[27, 64]

Other methods of indirect attack upon the injured duct are also of questionable value. There is no successful method of producing intrapleural tamponade by air or fluid.[68] Thoracotomy or thoracoplasty should be discarded. The injection of fibrinogenic agents is a blind and uncertain procedure. So far as drainage of retropleural chylomas is concerned, it would seem more logical to attack the duct directly, since the surgical exposure would be much the same. Roentgen-ray therapy might be of value if rupture of the duct were due to neoplasm.[52, 53]

INTRATHORACIC SURGICAL LIGATION OF THE THORACIC DUCT

We have been able to find only two recorded reports of surgical ligation of the thoracic duct in the chest for the treatment of chylothorax. The first of these[56] followed sympathectomy for hypertension. The patient was operated and the injured duct successfully ligated, but the patient died suddenly on the table. Chyle had been administered intrasternally without evidence of harmful effect in the preoperative period. Intravenous chyle was administered during the operation. Autopsy did not reveal the cause of sudden death.

Lampson[40] reported the second case. The cause of chylothorax in his patient was obscure, and was presumed to have been the result of strenuous coughing. His approach was through the left sixth rib bed. The duct was identified and ligated after incision of the mediastinal pleura anterior to the aorta, retraction of the esophagus anteriorly and the aorta to the left and posteriorly. One year following operation there has been no reaccumulation of chyle but his patient has great difficulty in maintaining her weight and there has been some residual fixation of the left chest.

Lampson mentions another case of successful ligation of the thoracic duct in the left chest by Dr. R. H. Meade, who approached the duct from behind the aorta, rather than from between the esophagus and the aorta. Lampson does not desire to report Meade's case, and does not include it in his historical review.

CASE REPORT—RHODE ISLAND HOSPITAL NO. 420265

Mrs. G. H., a 35-year-old housewife, was first admitted to the Rhode Island Hospital on December 10, 1941, complaining of headache of 2 years' duration. She was said to

have had high blood pressure since the birth of the last of her 3 children 12 years previously. Her father and mother had been hypertensive.

Physical examination revealed marked elevation of blood pressure and rather extreme obesity (181 pounds). Preoperative sedation and other tests indicated a possible favorable outcome from sympathectomy, which was performed by one of us (R. R. B.) in two stages, on December 19th, and December 29th, 1941. Subcostal incisions, with removal of the twelfth ribs, were made. The diaphragm was incised, and the sympathetic chain removed bilaterally from the tenth thoracic to the second lumbar ganglion. As much of the distal splanchnic nerves as could be secured through the small diaphrag-

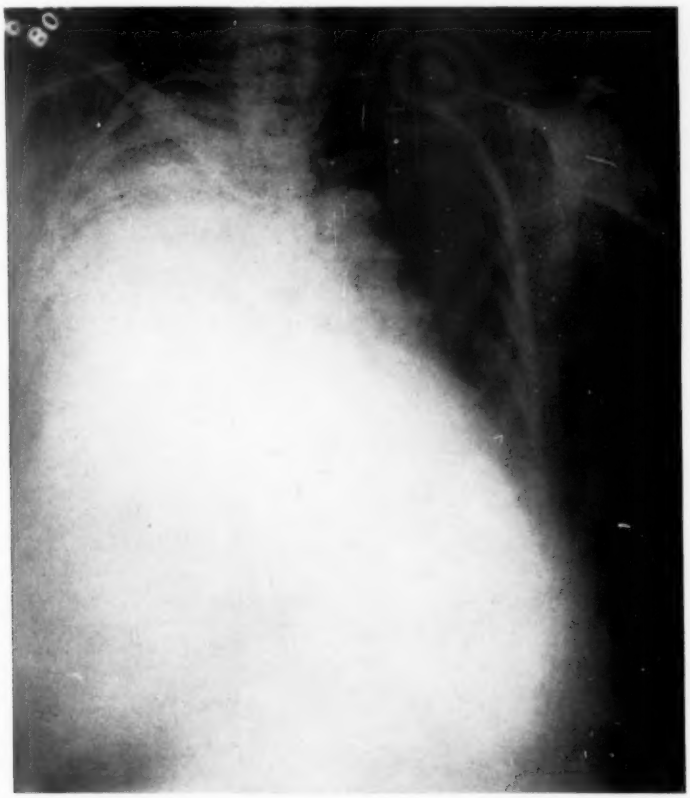

FIG. 1.—Chest X-ray taken before first paracentesis, demonstrating right chylothorax.

matic incisions used at that time were excised. The thoracolumbar nerve chains removed measured 12 centimeters in length and the splanchnics 8 centimeters. Renal biopsy revealed "no significant abnormality."

The patient was discharged much improved, with a satisfactory fall in blood pressure at rest, orthostatic hypotension, and complete relief of headache.

She was again admitted to the hospital 6 years later, on April 25th, 1947, complaining of increasingly severe headaches of 6 months duration. Her hypertension had recurred during the intervening years.

Physical examination demonstrated early retinal sclerosis (Grade II), moderate left ventricular hypertrophy and excellent renal function. Her weight was 180 pounds.

Sedation and other tests were again favorable and the patient was advised to accept extensive bilateral thoracic sympathectomy in two stages.

Second Operation.—On May 1st, 1947, a long vertical dorsolumbar incision was made on the right side, with the resection of two inches of the tenth and eleventh ribs near the spine. The posterolateral attachments of the diaphragm were incised down through the right crus and a wide exposure of the lower chest and upper retroperitoneal area made. Dense adhesions existed between the pleura and the diaphragm from the previous operation. There was no evidence of nerve regeneration except for a large neuroma of the great splanchnic nerve at about the level of the tenth rib. The thoracic chain and splanchnic nerves were removed to the mid-chest region, a biopsy was taken from the kidney, and the diaphragm and operative incisions closed.

Following operation the patient did so well that she was discharged on the eighth day, at her own request, with the understanding that she would return at a later date for sympathetic surgery on the left side. On the day of her discharge she walked easily,

TABLE II.—*Volume of chyle 32,180 cc. in 35 days. Accumulation of chyle began 10 days following injury of duct and ceased abruptly following ligation. Average protein concentration of the chyle was 3% and average concentration of lipids was 2.4%.*

RECORD OF CHYLE LOSS	
Days Post-Operative	Chyle Loss cc.
10	2,000
12	2,400
14	2,600
17	1,600
20	2,200
23	1,700
24	1,800
27	1,600
29	2,300
32	2,100
34	1,200
36	1,600
39	1,800
40	2,200
42	2,100
44	1,480
45	1,500
Total	32,180

without dyspnea. Her resting blood pressure was 145 millimeters of mercury systolic and 90 diastolic. Her breath sounds were reported as clear.

Third Admission.—Two days following discharge and ten days following sympathectomy the patient was returned to the hospital in a condition of collapse. She was cold, clammy and cyanotic. Breathing was rapid and labored. Her pulse was thready and elevated. Blood pressure in millimeters of mercury was 100 systolic and 80 diastolic and temperature was 98.0 degrees Fahrenheit. Immediate chest roentgenogram (Fig. 1) verified the clinical impression of fluid on the right side, and aspiration yielded 2000 cubic centimeters of pinkish-white fluid having the appearance and consistency of melted strawberry ice cream. Laboratory examination verified our impression that this fluid was chyle, not pus.

Clinical improvement following the first and many subsequent chest taps was dramatic. Respiratory and vascular collapse occurred once or twice each 48 hours, and before long the patient found herself requesting thoracentesis for relief of her symptoms.

The subsequent treatment and study of this patient was very difficult. Because of adiposity and thrombosis from her previous intravenous treatments, she had few accessible peripheral veins, and we were forced to rely for nutrition upon dietary measures alone. High caloric, high protein food, reinforced with casec eggnogs, were employed but in spite of heroic efforts on the part of the staff and the patient her course was progressively downhill. Table II demonstrates that a total of 32,180 cc. of chyle was removed from May 10th to June 14th with a serious daily loss of fluid, fat and protein. There were 17 chest taps. In spite of the high carbohydrate high protein diet her blood serum protein fell from 7 Gm.% to 4.2 Gm.% (Fig. 2), lymphocytes practically disappeared from her circulating blood (Fig. 3), and her weight fell from 182 to 168 pounds. Phrenic neurotripsy was performed under local anaesthesia on June 3rd, without benefit.

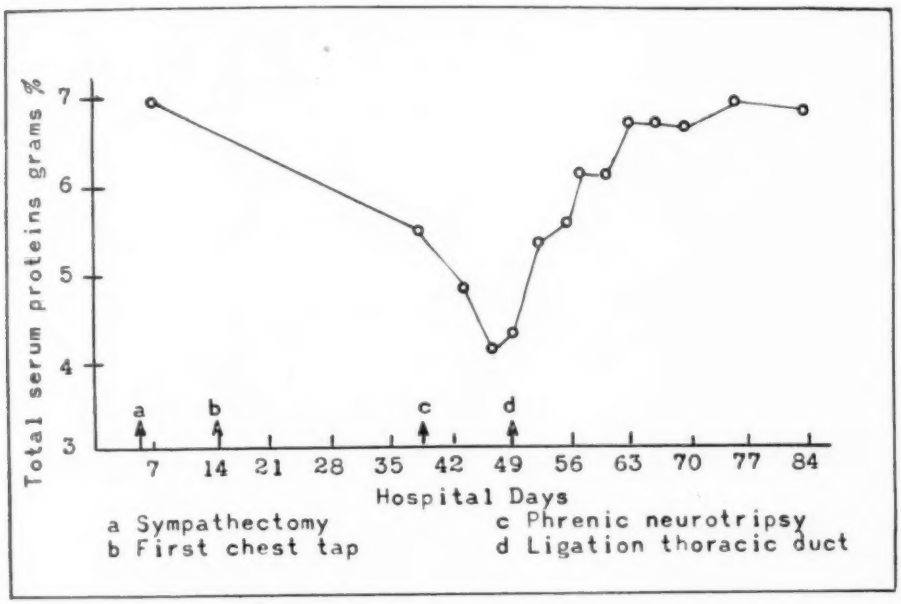

FIG. 2.—*The Course of Serum Protein Concentration.* During the phase of chylothorax an average of 919 cubic centimeters of chyle containing 28 Gm. (3 Gm.%) of protein were lost daily. Under these conditions, the serum protein concentration fell progressively and was not influenced by high protein diet or phrenic neurotripsy. Dramatic and prompt elevation in the protein concentration occurred with ligation of the thoracic duct.

Intravenous amigen, blood plasma and whole blood were finally administered and the patient was reoperated on June 14th, 1947. Eight ounces of heavy cream were given by mouth four hours before surgery.

Operation—June 14th, 1947.—The chest was entered on the right side after resection of the 8th rib. Fifteen hundred cubic centimeters of chyle were aspirated. After some search, a sinus from which chylous fluid could be seen flowing was discovered leading down through the crus of the right diaphragm.

The mediastinal and diaphragmatic pleurae were incised and the diaphragm sectioned along its posterolateral attachments. The upper abdominal aorta was gently retracted and the cisterna chyli exposed with surprising ease. The draining sinus was readily followed to this structure, where a semicircular rent about one millimeter long was discovered on its anterior surface (Fig. 4). It would have been technically feasible to

have sutured this opening, or to have occluded the rent with fibrin foam soaked in thrombin solution, a technic which has subsequently been employed by Smithwick.[67] We decided to run no risks of recurrence of chylothorax. Ligation of the intestinal and lumbar branches would not have prevented back flow from the descending thoracic trunks or from the main duct, all of which were clearly visible. We therefore ligated the lower thoracic duct, the bilateral descending thoracic, the bilateral lumbar, and the intestinal trunks. Additional security for the closure was provided by suturing a flap of mediastinal pleura and a strip of oxycel over the rent in the cisterna. The diaphragm and operative incisions were closed without drainage. Silk technic was used throughout.

The postoperative course of this patient was essentially uneventful. Small amounts of serous fluid were aspirated on two occasions from the anterior lower right chest, but there was no recurrence of her chylothorax (Fig. 5). Mild transitory edema of the lower extremities, no more than might have been accounted for on the basis of hypopro-

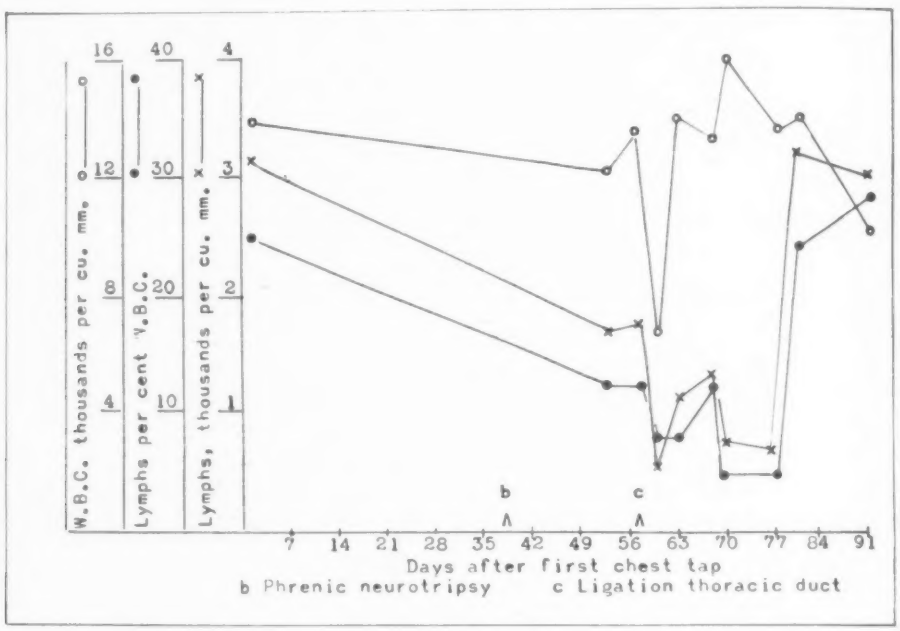

FIG. 3.—*A Demonstration of the Progressive Reduction of the Number of Lymphocytes.* The percentage of lymphocytes fell from 23 to 5 and the absolute number per cubic millimeter from 3151 to 675. The lymphocyte count was not influenced by phrenic neurotripsy, but, after a brief delay, responded to thoracic duct ligation.

teinemia, was noted during the first postoperative week. There was no clinical evidence of ascites at any time, either before or following operation and no enlargement of the peripheral lymph glands or the spleen. Figure 6 demonstrates cessation of chylothorax, satisfactory and rapid return of serum protein values and lymphocyte percentages to normal, and a slight but delayed gain in weight following ligation.

Studies of the percentage of eosinophiles in the peripheral blood demonstrated a fall from 4 per cent at onset of chylothorax to almost complete absence (1 per cent or none on several occasions). This reduction persisted after a return of the lymphocytes to normal levels.

The patient was discharged from the hospital on July 4th, 1947, twenty days following

ligation of the lower thoracic duct and obliteration of the cisterna chyli and its afferent trunks.

At the present time, six months following her last operation, she is in excellent health, free of headaches, and without evidence of fluid in her chest or abdomen. There is no peripheral edema. Her white blood count is normal; lymphocytes 22 per cent and eosinophiles 3 per cent. She is "dieting" and weighs 170 pounds.

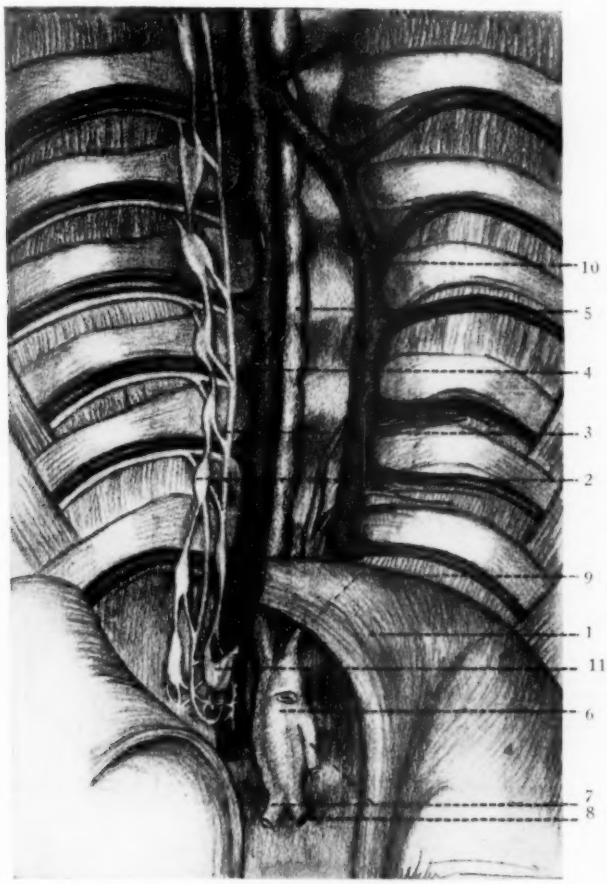

FIG. 4.—Artist's sketch demonstrating the relationships of the sympathetic nervous system in the lower right chest with the azygos vein and the thoracic duct. The cisterna chyli, with its bilateral lumbar and intestinal trunks are shown. The descending thoracic trunk on the left side, and the point of laceration in the cisterna are likewise demonstrated.

1. Diaphragm
2. Thoracic sympathetic chain
3. Splanchnic nerve
4. Azygos vein
5. Thoracic duct
6. Cisterna chyli
7. Lumbar trunks
8. Intestinal trunk
9. Descending thoracic trunk
10. Hemi-azygos vein
11. Celiac ganglion

DISCUSSION

In view of the present prevailing high mortality of traumatic chylothorax and the numerous treatments recommended, the unfortunate surgeon who bears responsibility for such a case may be naturally uncertain concerning his proper course of action. Assuming that conservative measures fail, what is his justification for surgical attack? If the thoracic duct be ligated, by what route does chyle and lymph find its way into the general circulation? Is ligation physiologically safe and technically feasible?

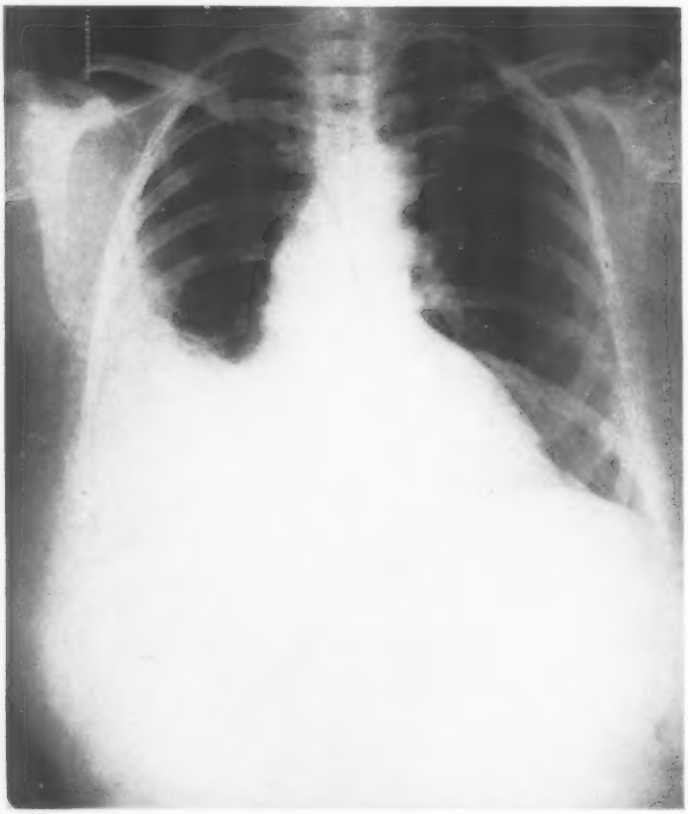

FIG. 5.—Chest X-ray taken July 10, 1947; three weeks following ligation. The pleura is thickened, but there is no recurrence of chylothorax.

It has been abundantly demonstrated, both clinically and experimentally, that the integrity of the thoracic duct is not essential to life. Numerous cases of occlusions of the duct or of the receptaculum chyli due to carcinoma, tuberculosis, cyst or fibroma, without the development of chylothorax or chylous ascites have been reported.[76] It is probable that when chylothorax does develop under these circumstances, it is due more to erosion and leakage from the duct, or to interference with drainage by way of collateral branches than to actual obstruction.[26]

Treatment of injuries of the thoracic duct in the neck has been discussed by numerous authors.[8, 18, 35, 39, 50, 77] Repair by suture or reimplantation into a vein has been advocated by some, but many successful cases of occlusion of the injured area by tamponade or ligature have been reported. In 1907 DeForest[18] said that a wounded thoracic duct should be treated exactly as a bleeding blood vessel,—by ligature, and Warschauer[73] even suggested the

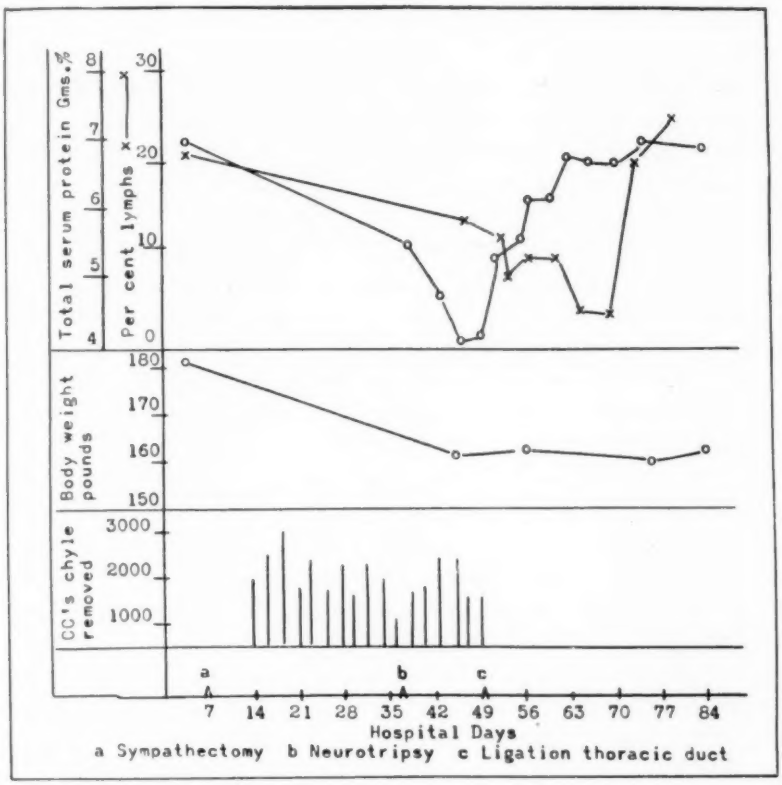

FIG. 6.—*A Demonstration of the Effect of Chyle Loss on Body Weight, Serum Protein Concentration and the Number of Circulating Lymphocytes.* The effects were not influenced by diet or phrenic neurotripsy. The response to thoracic duct ligation was a prompt elevation of the serum protein concentration, arrest of body weight loss and a gradual return to normal of lymphocyte percentage in the peripheral blood.

advisability of intentional ligation of the duct in all operations in the neck where it might be endangered.

In spite of the relatively high pressure developed within the duct following ligation there is extensive experimental[6, 13, 41, 43, 46, 50, 63] and clinical evidence[12, 15, 40, 54, 70] that rupture of the duct or of the cisterna chyli does not occur.

One of us (R. R. B.) has witnessed ligation of the duct on several occasions where it had been injured in the supraclavicular triangle of the neck during the removal of malignant glandular metastases. In no case has there

been any postoperative evidence of chylous accumulations or of metabolic disturbances.

To Lee[41] goes the credit for the most thorough and convincing elucidation of this matter. After a review of the literature he described experiments in which he was able to demonstrate absolute intrathoracic ligation of the thoracic duct in experimental animals for the first time. None developed chylous effusions. The animals were sacrificed at variable intervals and autopsies performed. "As a result of these dissections, two general types of collateral circulation were established. The one type consisted of a collateral circulation to the right thoracic duct;—the other type comprised those cases in which lymph entered the azygos vein or its branches."

Lee described edema about the large lymphatic trunks and cisterna chyli following ligation, hypertrophy of the intra-abdominal lymph glands, and contraction of the duct above the point of ligature. By injection methods he demonstrated lymphatico-venous anastomoses between the cisterna chyli and the azygos, left intercostal, and left lumbar veins. Retrograde injections demonstrated possible channels as far as the hilum of the kidney and the subserous coats of the intestine. Lee concluded that non-functioning embryonic anastomoses exist between lymphatic and venous systems, and that these channels are capable of enlarging and functioning after ligation of the thoracic duct.

That ligation of the thoracic duct does not produce chylothorax has been demonstrated by others.[6, 50] Yater[76] concluded that,—"Many cases of obstruction of the thoracic duct are not associated with the accumulation of chylous fluid because of the normal collaterals which empty into veins."

Blalock and co-workers,[6, 60] unable to produce chylothorax by ligation of the thoracic duct, found that this condition did develop in approximately one-half of their animals in which the superior vena cava had been occluded. If the death of these animals was prevented by repeated aspirations of chyle, frequently the lymph vessels would enlarge with the passage of time and the chyle would be returned to the venous system. They believe that there are lymphatico-venous communications in the peritoneal cavity.

On the basis of these considerations, when the patient with an injured thoracic duct presents a progressive downhill course, and conservative measures are failing, surgical ligation of the thoracic duct would appear to be a logical procedure.

Speculation as to how the cisterna chyli was injured in our case is fruitless. It was probably torn during the separation of retroperitoneal adhesions which had formed following the operation in 1941. From the clinical findings, we expected to find intrathoracic injury of the duct, not subdiaphragmatic injury of the cisterna. The recent operative suture line in the diaphragm probably provided a convenient point of perforation into the chest and explains the absence of chyloperitoneum.

It is interesting to speculate on the route by which lymph and chyle are finding their way into the blood stream of this patient. In view of the fact

that all main afferent channels to the cisterna chyli and lower thoracic duct were ligated, it would appear that lymphatico-venous anastomoses within the abdomen, rather than collateral lymphatic anastomoses to the proximal thoracic duct or to the azygos vein within the chest, must be in operation.

Whether or not delay of several weeks between injury and ligation of the major lymphatic vessels favors the establishment of a more adequate collateral circulation, as it does in such vascular conditions as arterio-venous fistulae, is unknown. In view of the fact that immediate ligation of the duct following recognized injury, either within the neck or the thoracic cavity, is being practiced by modern surgeons without the development of chylothorax,[12, 33, 54, 70] it would appear that adequate collateral circulation already exists, and that delay in surgical repair for the purpose of establishing collateral circulation is unnecessary.

Study of the anatomy of the thoracic duct demonstrates obvious reasons for the clinical fact that right-sided chylothorax occurs more often in low injuries of the duct and left-sided chylothorax in high injuries. Persistence of embryonic ducts resulting in abnormal anatomic variations probably explains apparent exceptions to this rule.

Surgical exposure of the lower thoracic duct through the right chest is not a particularly difficult procedure. The approach may be made by incision of the mediastinal pleura following thoracotomy, as in this case,—or by the usual retropleural approach utilized in resection of the splanchnic nerves for hypertension.

In view of the fact that the lower thoracic duct and cisterna chyli are the "focal points" for the collection of the major portion of the lymph and chyle and that fibrosis and occlusion of the duct usually occurs proximal to a point of ligation or obstruction, it is our opinion that low thoracic duct ligation through the right chest is not only indicated in right chylothorax but that it would probably also prove to be effective in the treatment of left chylothorax due to high injury of the main duct, where surgical exposure of the point of injury is more difficult and hazardous.

Ligation of the duct low in the right chest should theoretically markedly reduce or entirely prevent leakage of chyle from a more proximal point of perforation, and we see no reason why this measure should not be effective in the treatment of almost all types of chylothorax, regardless of etiology.

If bilateral symmetrical ducts or other congenital abnormality be suspected, surgical approach should be on the side of the chylothorax, where a sinus will be found leading to the point of injury.

A fat meal administered several hours before operation will stimulate the flow of chyle and facilitate discovery of the incontinent duct. This procedure was used in our case and chyle continued to flow until the ducts were occluded.

A study of our findings verifies the observations of others regarding the fall of lymphocytes and eosinophiles in the peripheral blood. It is our feeling that a serious incontinence of the thoracic duct cannot long exist without a rapid and progressive fall of these constituents, especially the lymphocytes.

The explanation of the reduction of lymphocytes is obvious but of the fall of eosinophiles is obscure.

Perhaps the most significant observations that have been made in our case concern the metabolism of protein in chylothorax and will be reported in greater detail elsewhere. In general they verify the observations of others regarding the difficulty, amounting to hopelessness, of maintaining adequate serum protein concentrations by dietary means in the presence of prolonged incontinence of the thoracic duct resulting in large serum protein losses. In spite of the fact that our patient consumed a minimum of 80 Gm. of protein daily, her blood protein progressively fell to dangerous levels. The fall was not influenced by phrenic neurotripsy. Following surgical ligation her protein level rapidly returned to normal without significant change in the diet.

Low protein values in chylothorax do not have the same significance as equally low values in patients suffering from hepatic failure, cancer, or diseases of the digestive tract, where there is a fundamental disturbance in protein genesis. Hypoproteinemia in chylothorax does not, *per se*, contraindicate surgery, but rather the reverse.

We do not imply that an effort should not be made to maintain nitrogen balance by high protein intake. Nitrogen balance is desirable, and can be maintained at or near normal levels in spite of large protein losses.

In view of the high mortality rates existing in chylothorax, the inadequacy of conservative treatment, and the many theoretical and practical arguments in favor of surgical ligation, it is difficult to understand the almost universal condemnation of this procedure to be found in the literature. Such a fatalistic attitude is probably based on the assumption that surgical ligation is technically impracticable when, as a matter of fact, the distal thoracic duct lies within a few millimeters of the right splanchnic nerves, removal of which have become a more or less common procedure.

A further objection to surgical ligation is probably based on the fact that most patients suffering from this condition rapidly develop low blood protein concentrations, reduced protein reserves and emaciation, and appear unable to withstand a major surgical procedure. It is our feeling that expectant and conservative treatment should be discarded within a reasonable time, before emaciation and cachexia supervene, and before the patient's condition is so extreme that major surgery is contraindicated.

SUMMARY AND CONCLUSIONS

1. A case of injury of the cisterna chyli during sympathectomy for hypertension, with cure of the resulting chylothorax by ligation of the thoracic duct, the cisterna chyli and all of its main afferent trunks, is described.

2. The literature of traumatic chylothorax is reviewed, and the causes, symptoms and treatment discussed.

3. The anatomy of the thoracic duct, the characteristics of chyle and the mechanics of lymph flow are reviewed.

4. Previously reported clinical, metabolic and blood cellular changes characteristic of chylothorax are verified.

5. Continuity of the thoracic duct and cisterna chyli are not essential to life, while incontinence of either is a serious hazard.

6. Lymphatico-venous anastomoses within the abdomen are adequate for the return flow of lymph and chyle following obliteration of the cisterna chyli and lower thoracic duct.

7. A period of delay between injury and operation may encourage collateral circulation of lymph and chyle, but delay of surgery for this purpose is not necessary.

8. The maintenance of normal metabolism, especially protein metabolism, by dietary methods is impossible in the presence of persistent severe chylothorax.

9. Hypoproteinemia in chylothorax is due to excessive protein loss, and is a strong indication for surgical treatment.

10. Injury of the cisterna chyli may result in chylothorax.

11. Injury of the thoracic duct and/or the cisterna chyli is a hazard of intrathoracic surgery, especially of sympathetic and esophageal surgery.

12. The prevention of chylothorax following surgical injury of the thoracic duct depends upon recognition of the injury and immediate repair or ligation.

13. Ligation of the lower thoracic duct should be effective in the treatment of most cases of left and all cases of right chylothorax, regardless of etiology.

14. Surgical approach to the lower thoracic duct and cisterna chyli should be through the right thorax.

15. Ligation of the thoracic duct and/or the cisterna chyli, when indicated, is feasible and may be a life saving procedure.

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RECTAL STRICTURE OF LYMPHOGRANULOMA VENEREUM*

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THERE HAVE BEEN SOME 130 ARTICLES written on lymphogranuloma venereum since 1925 dealing with various phases of the subject. The most controversial phase of the disease has been the treatment of the end result or tertiary stage. Its manifestation of severe intractable stricture involves the rectum and rectosigmoid. Occasionally the granulomatous process extends into the sigmoid and at times as far as the transverse colon. It may even show "skip areas" involving the rectum, skip the sigmoid and involve the descending colon.

Operative treatment has not yet become standardized. The literature contains numerous small series of cases and isolated case reports of various operative methods. There has actually been no evolution of basic surgical principles as yet. Some writers approach this problem from the inflammatory basis and tend to more conservative procedures, while others apply cancer principles and favor more radical operations. Where a systemic infection is present it is doubtful whether the latter principles can be considered applicable. Most authors agree on the value of colostomy preliminary to resection. However, its value in the elimination of the secondary infection and whether or not it paves the way for more conservative procedures has not been determined.

Hartmann[8] has had the most extensive surgical experience with this disease. At first he practiced external rectotomy, operating on 15 cases without a mortality. However, these cases continued to suppurate and many were incontinent. Following this he adopted a transanal excision of the stricture in three cases but gave up the procedure as results were unsatisfactory, due, he states, to leaving in the mucous membrane of the anal canal. Following this he began to use perineal excision, and later intra-sphincteric resection, eventually finding the latter the more satisfactory procedure. One death occurred among nine patients subjected to perineal excision and two deaths occurred in a series of 47 intrasphincteric resections. Abdomino-perineal resection was reserved by Hartmann for extensive cases only, and in six such cases there were three deaths.

DeRoche[5] reported 21 cases of excision of the stricture with one death. However, his results were poor, there being only three satisfactory results among eight patients followed for one year.

In 1933 Dimitriu and Stoia[6] reported 25 cases of abdomino-endoanal excision with preservation of the sphincter mechanism. Their method was an adaptation of a sphincter saving method of resection reported by Villard and

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Ricard[14] for the management of carcinoma of the rectum. The technic comprised a freeing of the sigmoid and rectum by laparotomy. The anus was then closed and a perineal incision made encircling the anus. Through this incision

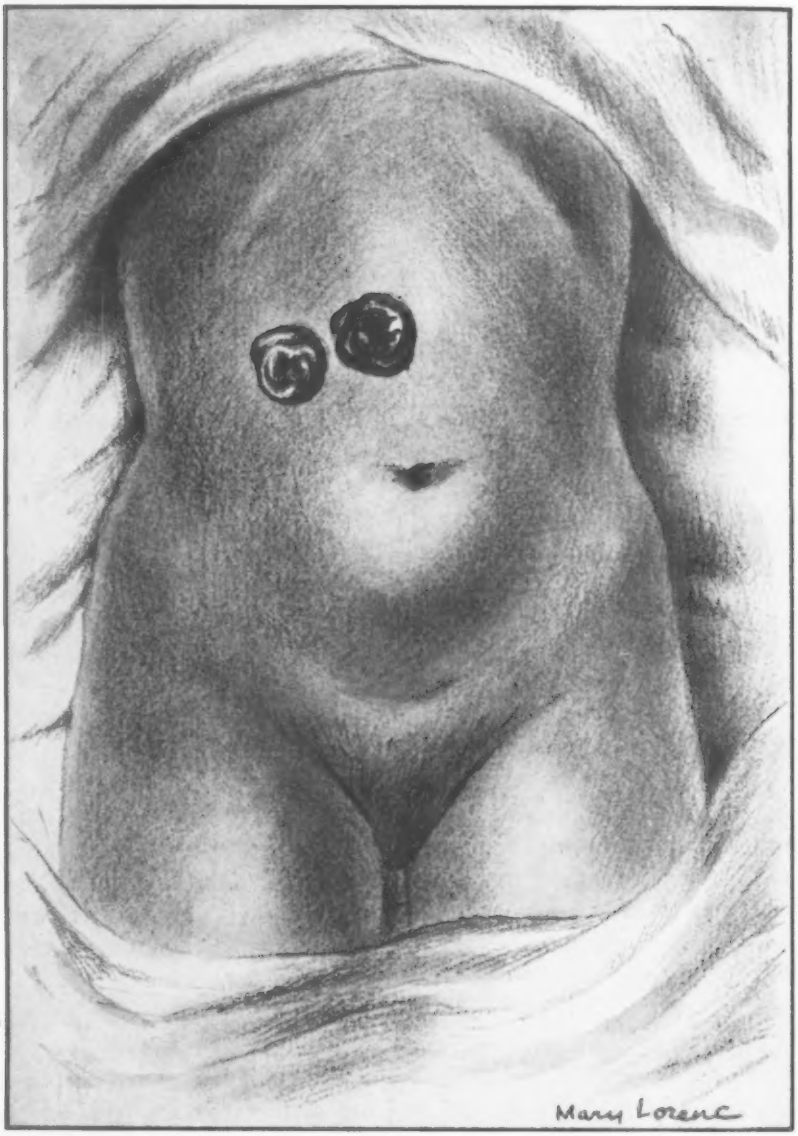

FIG. 1.—Defunctioning colostomy.

the sphincters were dilated and the rectum freed further until it could be pulled through the sphincters. The rectum was then amputated and the sigmoid pulled through the dilated sphincters and sutured to the skin. These

authors considered 19 cases cured by this method with three deaths and three recurrences. Colp[3] reported two cases in 1941 managed by this method.

In 1933 Keller[9] reported his experiences with tunnel skin grafts in the management of rectal strictures. Hair free grafts varying from one half to full thickness were sutured together to form a tunnel with the raw surface outward. A trocar and cannula were then passed through the stricture from the perianal region, and the cannula removed. A "U" shaped carrier passed through the anus, was inserted retrogradely through the cannula and used to pull up the graft. The trocar was removed and three more tunnel grafts inserted in a similar manner at equidistant points. Postoperatively these grafts were held in place by a Hagner or Pilcher bag. Two weeks postoperatively the tunnels were divided. For strictures of the anal canal the grafts were held in place by a mold of dental compound. Eight cases were reported with seven satisfactory results.

Lockhart-Mummery[10] favors excision of the stricture in the early cases with the Whitehead operation. For late cases perineal excision is advocated with due admonition concerning the technical difficulties.

David and Loring[4] reporting cases in 1936 recommend permanent colostomy, but state that cure is never obtained by this method. In 1937 Spiesman, Levy and Brotman[13] reported a study of 183 strictures from the Cook County Hospital. Only two of these patients came to operation, a permanent colostomy and posterior excision having been performed.

Edwards and Kindell[7] in 1938 reported six cases treated by the two stage Lockhart-Mummery method with one death, and mention four additional cases without a fatality. They emphasize the importance of laparotomy to determine the upward extent of the process. The second stage was performed from a few weeks to several months after colostomy, to allow patients to obtain maximum improvement in general condition.

Morris[11] reported one case in 1939 treated by abdomino-perineal resection of the strictured area. This patient had had a previous colostomy and when first seen the granulomatous process had involved the stoma. This necessitated preliminary resection of the colostomy stoma three months prior to abdomino-perineal resection.

In 1939 Warthen[15] reported a method of management in which the cul-de-sac was obliterated by the Moschowitz technic, and a left inguinal colostomy performed. The basis of this was the elimination of the hazards of dilatation by obliteration of the cul-de-sac, and putting the bowel at rest by diverting the fecal stream. Ten cases were reported with amelioration of the stricture but none of the cases had been completed.

Patterson[12] reported five cases in 1940 treated by permanent colostomy, and a second stage stripping out of mucous membrane from the lower sigmoid and rectum. At the time the colostomy was performed, all acute abscesses and fistulae about the anus were opened. The second stage was carried out several weeks after the colostomy.

Bacon[1] in 1941 agreed that radical extirpation is the procedure of choice.

TABLE I*†

No.	Name	Age	Sex	Color	Involvement	Operations	Date	Result
1.	B.A.	33	F	C	Stricture 2 cm. above anus.	1. Colostomy.	9/24/41	
						2. Resection of stricture, end to end anastomosis of rectum.	3/18/42	
						3. Closure of colostomy.	10/27/43	Good
2.	C.B.	42	F	C	Stricture 4 cm. above anus.	1. Colostomy.	7/15/42	
						2. Abdomino-perineal resection rectum end to end anastomosis of sigmoid to anal canal.	6/23/43	
						3. Closure of colostomy.	11/7/43	Good
3.	L.C.	31	F	C	Stricture 5 cm. above anus.	1. Colostomy.	12/16/41	
						2. Resection of stricture, end to end anastomosis of rectum.	10/24/42	
						3. Closure of colostomy.	3/31/43	Good
4.	L.S.	50	F	C	Stricture 3 cm. above anus.	1. Colostomy.	12/4/41	Good
						2. Perineal resection unsuccessful.	11/4/42	Died 1 year later, Ca. stomach.
						3. Abdomino-perineal resection, end to end anastomosis of sigmoid to anal canal.		
						4. Closure of colostomy.	3/9/43	4/26/44
5.	F.G.	25	F	W	Stricture 4 cm. above anus.	1. Colostomy.	7/17/44	
						2. Resection of stricture, end to end anastomosis of rectum.	6/15/45	
						3. Closure of colostomy.	4/30/47	Good
6.	M.S.	34	F	C	Stricture 3 cm. above anus, multiple fistulae with slough of perineal body, and anus opening 1 cm. from vagina.	1. Colostomy.	6/14/44	
						2. Resection of stricture, end to end anastomosis of rectum.	1/3/45	Recurrence
						3. Abdomino-perineal resection of rectum, end to end anastomosis of sigmoid to anal canal.	1/29/47	
						4. Closure of colostomy.	7/30/47	Good
7.	L.S.	26	F	C	Stricture 2.5 cm. above anus.	1. Colostomy.	3/31/42	
						2. Resection of stricture, end to end anastomosis of rectum.	3/31/43	
						3. Closure of colostomy.	9/15/43	Good
8.	A.W.	48	F	C	Stricture 2.5 cm. above anus. Colostomy performed elsewhere.	1. Resection of stricture, end to end anastomosis of rectum.	5/22/46	
						2. Closure of colostomy.	6/26/46	Obstruction
						3. Cecostomy.	7/1/46	
						4. Plastic revision of colostomy closure.	11/13/46	
						5. Closure of cecostomy.	1/15/47	Good
9.	C.B.	28	F	C	Stricture 4 cm. above anus.	1. Colostomy.	5/29/46	
						2. Resection of stricture, end to end anastomosis of rectum.	10/30/46	
						3. Closure of colostomy.	4/15/47	Good

* Follow-up on these patients to July 1948.

† 16 of these cases are from the Fourth Surgical Division, Bellevue Hospital—Dr. A. S. McQuillan, Director.

1 case from Post-Graduate Hospital—Dr. J. W. Hinton, Director.

1 case from Beth David Hospital—Dr. F. W. Bancroft, Director.

TABLE I. (Continued)

No.	Name	Age	Sex	Color	Involvement	Operations	Date	Result
10.	I.G.	43	F	C	Stricture 2 cm. above anus involving distal 2/3 of sigmoid.	1. Colostomy.	5/22/46	
						2. Perineo-abdominal resection of rectum and distal 2/3 of sigmoid.	3/13/47	
						3. Descending colon and transverse colon rotated to L.L.Q.	5/16/47	
						4. End to end anastomosis of sigmoid to anal canal.	2/24/48	Good
11.	R.M.	34	F	C	Stricture 3 cm. above anus.	1. Resection of stricture, end to end anastomosis of rectum.	1/17/47	Good
12.	A.E.	42	M	W	Stricture 2 cm. anus extending to splenic flexure.	1. Colostomy.	11/27/46	
						2. Perineo-abdominal resection of rectum, sigmoid, and descending colon, with mobilization and rotation of transverse colon.	1/22/47	
						3. Anastomosis of transverse colon to anal canal.	1/24/47	
						4. Closure of colostomy.	6/25/47	Fair
13.	C.W.	32	F	C	Stricture 2.5 cm. above anus involving entire rectum, with skip area involving descending colon up to splenic flexure, where acute perforation was present.	1. Colostomy.	1/14/47	
						2. Exploration for subphrenic abscess.	1/22/47	
						3. Resection of descending colon.	3/19/47	
						4. Resection of stricture, end to end anastomosis of sigmoid to anal canal.	4/16/47	
						5. Closure of transverse colostomy by anastomosis of its stoma to the sigmoid.	9/12/47	Good
14.	M.M.	31	F	W	Stricture 3 cm. above anus.	1. Colostomy.	7/1/47	
						2. Resection stricture, end to end anastomosis of rectum.	7/16/47	
						3. Closure of colostomy.	8/27/47	Good
15.	P.P.	25	F	W	Stricture 2 cm. above anus extending to sigmoid.	1. Colostomy.	5/7/47	
						2. Attempted perineal resection of rectum.	8/20/47	
						3. Abdomino-perineal resection of rectum, end to end anastomosis of sigmoid to anal canal.	9/24/47	
						4. Closure of colostomy.	11/5/47	Undetermined. Schistosomiasis in specimen
16.	J.H.	38	M	W	Stricture 4 cm. above anus.	1. Colostomy.	8/16/46	
						2. Resection of stricture, end to end anastomosis of rectum.	9/22/47	
						3. Closure of colostomy.	11/4/47	Good
17.	H.G.	23	F	C	Stricture 2 cm. above anus.	1. Perineal resection of stricture, end to end anastomosis of rectum.	10/22/47	Good
18.	R.A.	48	F	C	Stricture 3 cm. above anus, extending to peritoneal reflection. Sigmoid-colostomy performed elsewhere 10 years previously.	1. Colostomy.	10/16/47	
						2. Resection sigmoid-colostomy and end to end anastomosis of sigmoid. Resection of stricture, end to end anastomosis of rectum.	10/30/47	
						3. Closure of colostomy.	1/29/48	Good

He stated however, that procedures involving division of the peritoneal floor will give a mortality of 65 to 80 per cent. He preferred management by the two stage Lockhart-Mummery procedure. After the performance of celiotomy and abdominal colostomy, the bowel was irrigated and the patient's general condition allowed to improve. The perineal resection was then performed. In 24 cases so treated, there were no fatalities.

Barber and Murphy[2] reported 35 resections in 1941. Four of these were sacroperineal resections and 31 were treated by abdominal colostomy, followed by sacroperineal resection. The hospital mortality in this series was 14.3 per cent. Their early efforts attempted sacroperineal excision with a permanent sacral anus, but inability to estimate sigmoidal involvement made preliminary celiotomy and abdominal colostomy necessary prior to sacroperineal resection. Exploration and colostomy were performed 10 days prior to resection. They objected to anastomosis of the rectum on the basis that the narrowing at the anastomosis site is as troublesome as the original stricture. This has not been our experience.

Woods and Hanlon[16] analyzed 192 cases from the Cincinnati General Hospital in 1942 and corroborated the inefficacy of colostomy alone. Abdomino-perineal resection was done on 23 cases, and a perineal resection on nine cases without a fatality. Their experience led them to favor abdomino-perineal resection as the operation of choice.

In 1946 Wright[17] et al reported 26 cases operated upon by Pauchets' technic. This was a sphincter saving technic resembling that of Villard and Ricard. Colostomy was done prior to resection. Three deaths occurred in this series. Follow-up of 12 cases showed cure in all except one who had draining sinuses secondary to bone involvement.

Since previous papers have extensively described all the phases of this disease, its etiology, the primary and secondary stages, etc., we will not repeat but instead confine our discussion to the end resulting granuloma affecting the lower colon, rectosigmoid and rectum. This phase has a controversial aspect since there are so many methods of treatment suggested. The attempt should be made to eradicate the granuloma and restore the patient to normal function since we are dealing with a young age group.

The age group ranges from 20 to 40 and the colored female is most often affected. We have had a few cases in the white female and a few in the male both colored and white. All of the strictures seen in our clinic have been caused by lymphogranuloma venereum. The only other cases of stricture have had as the etiology previous anal or rectal operative procedures resulting in stricture. The stricture of lymphogranuloma venereum begins within 3 to 5 cm. of the anorectal or mucocutaneous line and goes proximally for variable distances.

The virus enters the perianal and perirectal tissue by the lymphatic route from the primary lesion in the vagina and from the inguinal lymph nodes. The perirectal and intramural lymphatics become involved and this in turn causes the inflammatory process to involve the mucosa, submucosa and muscularis

forming a firm, hard tube which by maturation of the fibroblasts causes severe contracture and stricture formation. The mucosa loses all its identity. The area is thickened and as hard as cancer tissue. The stricture tube is completely fixed by fibrous tissue to all the surrounding structures. Above the stricture

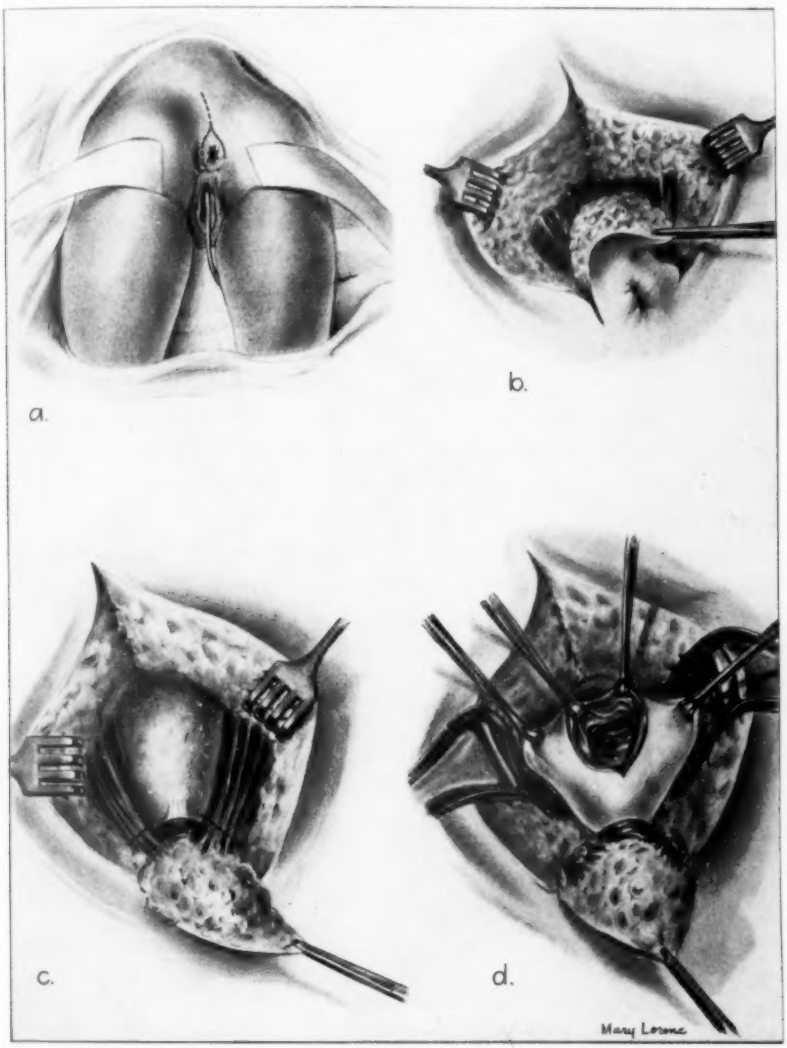

FIG. 2.—A. Position of patient and incision. B. Exposure of levator ani muscles. C. Division of levators. D. Incision of fascia propia.

ulceration from secondary infection occurs causing intractable diarrhea. Fistulae form to the perianal areas and ischiorectal fossae. At times fistulae into the vagina with slough and erosion of the perineal body result in cloaca formation between the vagina and rectum. There are often hypertrophy and fibrosis of the perianal tissue and fistulae about the skin which result from long drawn out chronic inflammation.

Histologically the mucous membrane is replaced by granulation and fibrous tissue. The mass has a chronic inflammatory exudate in which the predominating cells are lymphocytes, plasma cells and foreign body giant cells. Polymorphonuclears are present due to added acute and subacute inflammation. There are no areas with tubercle formation although at one time before 1925 many of these lesions were diagnosed as tuberculosis or syphilis. This phase of the disease then is a chronic granuloma similar to other granulomata of the intestinal tract. The scarring and stricturing are irreversible processes and will not respond to any form of medical or conservative surgical treatment. One case P. P. No. 15 showed the usual pathologic changes plus eosinophilic abscesses suspicious of schistosomiasis.

The symptoms depend on the extent and degree of stricture, and on the amount of secondary infection present. The typical patient is a poorly nourished exhausted colored female. The abdomen shows varying degrees of distention depending on the tightness of the stricture. The chronic obstruction is manifested by distention, crampy pains and intractable diarrhea. The blood count shows secondary anemia and usually slight leucocytosis due to secondary infection. The plasma proteins are low and the albumin globulin ratio may be reversed. The Frei test is always positive. There is a high percentage of these patients with positive serology for syphilis as a complicating factor.

The stricture begins 3 to 5 cm. above the mucocutaneous line and runs proximally, usually ending at the rectosigmoid or low sigmoid area. Two of our cases extended to the transverse colon. One case extended to the sigmoid, then skipped an area in the descending colon for about six inches and continued on from there to the transverse colon.

The stricture results in two conditions which predicate the method of therapy selected. Functionally the lesions cause chronic obstruction, or occasionally acute obstruction. Secondly pyogenic infection accompanies the local lesion and contributes to the poor general condition of the patient. It is to these conditions that the surgeon must devote his efforts.

The first principle is the eradication of the secondary infection, and restoration of the patient to normal physiology. To accomplish this a completely defunctioning colostomy is done. It is performed 5 to 7 days after admission. In two cases, No. 11 and No. 17, where secondary bacterial invasion was not severe and no fistulae existed it was possible to do a complete resection and anastomosis in the perineum without the benefit of colostomy. This however, is unusual.

The change that occurs is almost unbelievable—the fistulae heal, the secondary infection clears up completely and the patients eat well, resulting in restoration of serum protein levels to normal, the return of normal albumin-globulin ratio and marked gain in weight with improvement in secondary anemia.

The second principle is the removal of the local focus. Cancer surgery requires radical excision but since this is only a granuloma based on virus infection its focus can be conservatively eliminated by excision of the involved

rectum or colon. A complete block dissection is not necessary. The sphincter is retained and the bowel continuity is reestablished. Lastly, the colostomy is closed and the patient is then completely rehabilitated with a normal functioning intestinal tract.

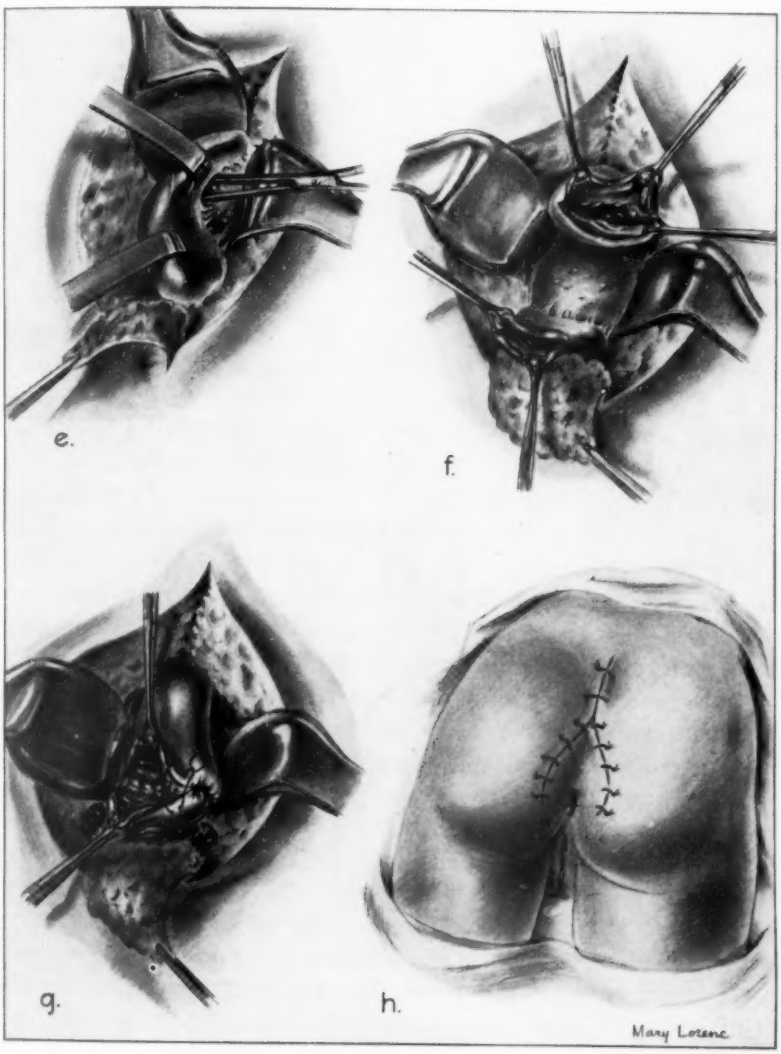

FIG. 3.—E. Mobilization of rectum and separation from vagina anteriorly. F. After resection of strictured area. G. Method of anastomosis. H. Closure of wound.

After complete healing the site of anastomosis just proximal to the sphincter shows a thin, slightly constricted area through which the finger can easily be pushed. It does not interfere with function and since all infection has been cleared away, this area does not change after healing has taken place.

TECHNIC

The defunctioning colostomy is performed through a transverse incision midway between the umbilicus and the costal margin, extending from the midline to the lateral border of the right rectus muscle. All structures are divided transversely. The transverse colon is lifted out and cleared of omentum and appendices epiploica for a distance of three inches. The mesocolon is opened between the bowel and the marginal artery obtaining a defect 2.5 cm. in diameter. The bowel is divided between Kocher clamps with a carbolic knife. The abdominal wall is closed in layers between the divided bowel ends. The bowel is secured by suturing appendices epiploica to peritoneum, muscle, and fascia. For further security one suture is placed through the parietal peritoneum grasping an avascular spot in the transverse mesocolon so that no internal hiatus is left between the loops. A dressing is applied about the Kocher clamps to hold the two loops 4 cm. above the skin level. The proximal clamp is removed within 36 to 48 hours.

The second stage is performed one to six months later depending upon the elimination of secondary infection and the condition of the patient. The patient is placed in the prone position with the hips flexed and the buttocks held apart by adhesive. An inverted "Y" incision is made beginning over the lower end of the sacrum extending to either side of the anus to the level of a line bisecting the anus transversely. This is deepened through the skin and subcutaneous tissue to divide the levator ani muscles posteriorly, thus forming a flap which may be reflected anteriorly when the fascia propria of the pelvis or presacral fascia is incised. The rectum and rectosigmoid are then mobilized from the anterior structures (vagina, or prostate and seminal vesicles) from the promontory of the sacrum to the internal anal sphincter. The rectum is divided transversely above the stricture and just above the internal sphincter. The proximal end of the rectum is anastomosed to the anal canal using one posterior layer of interrupted medium cotton sutures and two anterior layers of the same material. The anterior layers consist of an inner layer of interrupted Connell sutures and an outer layer of Halsted sutures. The flap is replaced and the wound is repaired with interrupted cotton sutures without drainage.

The third stage is closure of the colostomy and is performed four to six weeks after resection when the anastomosis and posterior wound are well healed. Preoperative preparation consists of five days on a low residue diet and 3 Gm. of succinyl sulfathiazole every four hours. The transverse incision is reopened and the bowel ends dissected free. The peritoneal cavity is entered and the adhesions about both loops separated. Sufficient bowel is then excised from each loop to allow accurate approximation and a two layer end to end anastomosis with interrupted medium cotton sutures is performed. The mesenteric defect is sutured and the wound closed in layers.

DISCUSSION

The technic described is adequate for most cases but in those where the lesion has extended more proximally in the colon or in the case of skip areas

it is necessary to open the abdomen to resect the involved area. The bowel proximal to the site of resection is then brought down to the pelvis and the abdomen is closed. At the same sitting or at another stage the perineal dissection is done and the end of the proximal colon is anastomosed to the anus just above the sphincters. In two cases, No. 6 and No. 17, the anal canal was so involved that its mucous membrane had to be excised. The sphincters were incised posteriorly and the rectosigmoid pulled through the anus.

We should be remiss if some of the difficulties of the described operations were not emphasized.

The colostomy offers no difficulties in performance but after its closure the transverse defect of the abdominal wall may be difficult to approximate. However, if the table is jackknifed the peritoneum and fascia may be brought together without tension. There have been no incisional hernias in this series despite this difficulty. There has been one obstruction following colostomy closure due to technical errors.

The perineal resection has offered many difficulties with other surgeons as one can glean from the literature but they are not insurmountable. The rectum and rectosigmoid are cemented to the surrounding tissue and sharp dissection must be used throughout to separate them from the vagina or prostate. At times dissection from the sacrum is like cutting through eburnated bone. Bleeding can be troublesome as ooze predominates. Fortunately this is controlled when the soft part flap is sutured back into place. A transfusion of 500 cc. to 1000 cc. of whole blood should be given during this procedure.

The proximal extent of the lesion is not always ascertainable before operation. Barium enema is often not possible as the patient cannot retain the barium. It is usually impossible to get a proctoscope through the stricture to see how far it extends. Valuable information can be obtained by the introduction of the barium suspension into the distal loop of the colostomy. Sometimes after perineal dissection has been started one finds that involvement extends above the promontory of the sacrum and abdominal dissection is necessary to complete the excision. As the entire diseased segment must be removed to effect a cure, high resection up to and including part of the transverse colon may be necessary. This is easily accomplished but bringing the proximal end down to the anus requires extensive mobilization. Two cases in this series illustrate this point:

Case 12.—A. E., male, age 42, white, admitted November 16, 1946, complaining of purulent rectal discharge, constipation and incontinence. Examination showed him to be poorly nourished. There was a tubular stricture of the rectum beginning at the internal sphincter. Roentgenologic examination showed a tubular narrowing of the rectum, sigmoid and descending colon up to the splenic flexure. The Frei test was positive. After a defunctionalizing colostomy had been performed there was a gain of 20 pounds in weight. The rectum was freed through a sacral incision, and then the abdomen entered through a low transverse incision. The rectum, sigmoid and descending colon up to the splenic flexure were resected and the distal end of the transverse colon mobilized and buried beneath the newly constructed pelvic floor. Two days later the posterior wound

was reopened and the transverse colon anastomosed to the anal canal. The latter was accomplished with more tension than had been anticipated and during healing there was separation of the anastomosis on its posterior aspect. However, despite a tubular narrowing at the anastomosis site due to this, colostomy closure was accomplished without incident. He now has normal bowel movements with continence of gas and feces.

Case 13.—C. W., female, age 32, colored, admitted January 14, 1947, complaining of abdominal pain, diarrhea, and distention of the abdomen for 24 hours. For the preceding four years she had noticed ribbon stools, constipation and rectal discharge. Examination showed a cachectic female in acute shock. The abdomen was distended, board-like and tender all over. On rectal examination there was a tubular stricture beginning just above the internal sphincter. There was a leucocytosis of 21,000 with 92 per cent polymorphonuclear neutrophiles. Upright abdominal films showed free air beneath the diaphragm and large bowel distention with fluid levels. Upon exploration there was free cloudy fluid coming from the left upper quadrant where a perforation was present just proximal to the splenic flexure. The large bowel was distended up to that point and collapsed distally. A transverse colostomy was performed. Convalescence was stormy and the right subphrenic space was explored for an abscess without positive findings. When her condition had improved, barium enema showed an ulcerative process involving the rectum, part of the sigmoid and the descending colon, one portion of the sigmoid being uninvolved by the process. Through a left transverse incision the splenic flexure, descending colon, and involved sigmoid were resected, planting the proximal end of the normal sigmoid in the lateral angle of the wound. One month later the rectum was resected and the normal sigmoid anastomosed to the anal canal. Gastro-intestinal continuity was reestablished by anastomosing the colostomy stoma to the proximal end of the sigmoid.

The anastomosis in the perineum is not difficult. The area is well exposed so that it may be done accurately. There have been no fistulae resulting from this anastomosis. The closure of the perineum usually results in primary union and drainage has not been necessary. Continence is established after this type of procedure.

All of these patients with completed operation have been restored to normal health. The intestinal tract is intact, there is complete sphincter control and fistulae are solidly healed. There is no protruding mucous membrane to cause constant moisture. The results have justified the extensive procedures.

The morbidity fortunately has been insignificant even in those cases where extensive colonic resection had to be done in stages in order to shift segments of the colon nearer to the pelvis for an anastomosis to the anus. In one case cited where the transverse colon was brought down and anastomosed to the anus, the posterior portion of the suture line pulled apart slightly and filled in with fibrous tissue but a good continuity of mucous membrane was established.

We are convinced that a complete resection of the diseased area results in cure. In Case No. 6 the point is illustrated. She was resected perineally and after healing a new tubular stricture promptly formed completely closing the bowel. At the second operation the resection was carried higher removing the entire rectum and pulling the sigmoid through the anus. Since the entire diseased segment has been excised there has been no recurrence.

There have been no fatalities in the 18 patients subjected to resection. Two of these patients are awaiting closure of the transverse colostomy.

SUMMARY

1. The rectal stricture of lymphogranuloma venereum is a common disease in a large city hospital especially among the negro race.

2. The surgical principles of management of chronic granulomata are applicable namely, physiologic rest of the part, extirpation of the diseased segment, and restoration of intestinal continuity.

3. A completely defunctioning type of colostomy is the first phase of treatment.

4. Perineal excision and primary anastomosis has proven an efficient method of extirpating the granuloma.

5. Extensive excision of the granuloma may be necessary, even as far as the transverse colon with anastomosis of this segment to the anus.

6. This method has been used in 18 cases with low morbidity and no mortality.

7. Arrest of the process and sphincter control have been achieved in all cases.

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TETRAETHYL AMMONIUM CHLORIDE—ITS EFFECTS ON SURFACE TEMPERATURES OF EXTREMITIES IN PERIPHERAL VASCULAR CONDITIONS*

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THE PURPOSE OF THIS ARTICLE is to report the effects of tetraethyl ammonium chloride on the surface temperatures of extremities. It shows that these effects are unsuitable as diagnostic criteria in peripheral vascular disease. The experiments which led to this conclusion were carried out as follows:

For the satisfactory clinical estimation of vasoconstrictor tone in extremities, one must have a method upon which he may rely to give a true, complete and dependable vasoconstrictor paralysis. The test should be, if possible, ambulatory and able to be completed at one sitting. The reports of Berry, Campbell, Lyons, Moe and Sutler,[1] gave hope that injections of tetraethyl ammonium chloride, by producing "autonomic blockade," would replace previous methods of estimating the vasoconstrictor element in peripheral vascular disease. If the drug were efficacious, it would furnish the desired data simultaneously on all four extremities, eliminating the discomfort attending blocking peripheral nerves, or the danger and discomfort of subarachnoid block. The present study was made for the purpose of comparing the surface temperature effects of the drug with that produced by peripheral nerve block. The latter method has been proven accurate and dependable over a long period and in many hands, and in the personal experience of the author with over 400 vasomotor studies.

A group of patients suffering from various types of peripheral vascular and central nervous system disorders were used as subjects. Food, drink and tobacco were ordered eliminated on the morning of the test. Each patient was placed recumbent for one hour or more in a specially constructed constant temperature room, with the lower extremities exposed from the upper thighs to the toes, and the upper extremities from the upper arm to the fingers. The temperature of the room did not vary significantly throughout the individual experiment, but the room temperature varied with the different subjects from 16.7° C. to 20° C. The surface temperatures of all four extremities were then measured at certain definite areas with the Tycos Dermatherm. A 10 per cent aqueous solution of tetraethyl ammonium chloride (100 mg. per cc.) was then injected intravenously over a period of from one to seven minutes. Two hundred mg. of the drug were used cautiously in the first case, but in the remainder, the drug was administered until the pulse *volume* showed a marked

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decrease, or until 500 mg. had been given. In some, its administration had to be slowed or temporarily discontinued while the weakened pulse volume returned to normal. The doses of tetraethyl ammonium given are as shown in Chart I. All but one patient received 300 mg. or more. In Cases 3 and 4,

Comparative Effects of TEAC and Peripheral Nerve Block on Surface Temperatures

F.M. Age 68 M. Arteriosclerosis Hypertension

Upper Extremities

	After 135" Exposure		Max. After TEAC		Max. After Block	
	R	L	R	L	R	L
Digit 1	20.9	20.4	21.0	21.0	30.4	30.7
2	20.0	20.4	21.0	20.5	30.4	30.8
3	19.9	20.0	21.0	20.7	30.7	30.9
4	19.9	19.9	21.0	20.9		
5	20.1	20.3	20.9	20.8		
Palm	22.5	23.0	23.1	22.7		
Dorsum	23.0	22.8	22.5	22.0		
Wrist	24.9	24.6	24.0	23.2		
Midforearm	26.9	26.9	25.5	25.6		
Below Elbow	27.9	27.8	27.7	26.7		
Above Elbow		27.4		26.5		

Lower Extremities

	After 135" Exposure		Max. After TEAC		Max. After Block	
	R	L	R	L	R	L
Digit 1	21.7	21.8	25.3	25.3	30.4	30.8
2	21.1	21.3	24.8	25.3	30.3	29.2
3	20.8	21.2	25.3	24.5	30.2	29.8
4	21.2	21.2	23.3	25.1*	30.2	30.7
5	21.2	21.7	21.8	23.8	29.8	29.8
Sole	24.2	23.8	23.5	23.6		
Heel	23.2	23.3	22.5	22.5		
Ankle	26.8	26.2	25.8	23.4		
Midleg	27.4	27.3	26.5	26.3		
Below Knee	25.8	25.3	24.8	23.8		
Above Knee	27.9	26.8	26.8	26.8		

FIG. 1.—F. M. Peripheral arteriosclerosis. Surface temperature after exposure, maximum surface temperature after tetraethyl ammonium and after nerve block. Note that in the upper extremities after tetraethyl ammonium there were no significant rises but after median nerve block all of the areas reached normal vasodilatation level. In the lower extremities after tetraethyl ammonium there were slight to moderate rises, whereas, block produced high sub-maximal temperatures. For further details of history and examination, see text.

the original dose of 300 mg. was supplemented by an additional dose of 200 mg.; in Case 6, 300 mg. were given as a second dose following an initial dose of 200 mg. These secondary doses had no apparent effect. When the administration of the drug was completed, the surface temperatures of all four extremities were measured at the selected sites at intervals of approximately five to ten minutes, in some for 30 minutes, in others until each individual site reached its maximum temperature. Without changing the position of the patient or the temperature of the room, vasoconstrictor paralysis was then produced at the same sitting in many extremities by procaine nerve block. Surface temperatures of the blocked zones were then measured at 10-minute intervals until each site reached its maximum temperature.

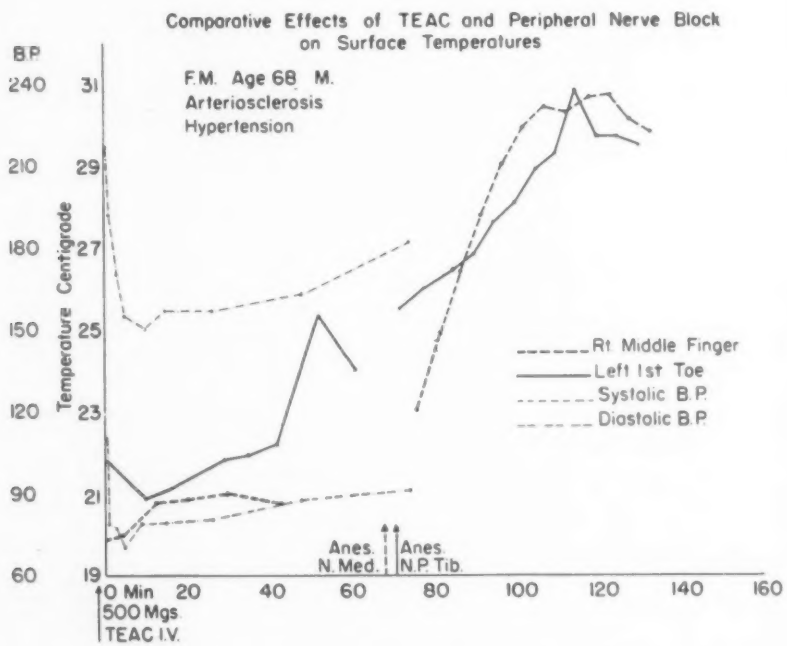

FIG. 2.—Same experiment as Fig. 1. The graph shows the results of the experiment in a single digit of the upper and lower extremities. After tetraethyl ammonium, the finger showed no significant change. The toe had an initial fall followed by a rise of 25.3° C. After nerve block, both finger and toe reached the normal level.

Of the total of 18 patients tested, nine were selected to be the subject of this report. The remainder are all cases of degenerative arterial disease and will become the material for an additional publication. The surface temperature effect of tetraethyl ammonium was measured in all 36 extremities in these nine patients; in 21 of these 36 extremities the effect was compared with that produced by novocaine block of the median or posterior tibial nerve; in one extremity, with block of the lumbar sympathetic chain. In one case the effect of tetraethyl ammonium was noted in the sympathectomized lower

extremities. It should be noted that in Cases 1, 4, 5 and 6, there was no evidence of arterial disease and normal responses to complete vasoconstrictor paralysis were to be expected. A similar result was also looked for in the upper extremities of all the cases except Case 2, since with this exception they showed no clinical evidence of arterial disease.

The maximum surface temperatures of the digits after the administration

Comparative Effects of TEAC and Peripheral Nerve Block on Surface Temperatures

R.B. Age 52 M. Thromboangiitis Obliterans

Upper Extremities

	After 50" Exposure		Max. After TEAC		Max. After Block	
	R	L	R	L	R	L
Digit 1	24.2	24.5	29.6	29.4	30.9	30.5
2	24.2	23.3	30.3	28.7	31.0	30.1
3	22.6	22.4	29.0	29.4	31.0	31.8
4	22.9	22.0	28.5	27.8	30.3	31.8
5	22.3	22.1	28.6	28.7		
Palm	27.4	27.8	30.1	29.9		

Lower Extremities

	After 90" Exposure		Max. After TEAC		Max. After Block	
	R	L	R	L	R	L
Digit 1	21.0	19.9	23.1	22.5	31.5	30.7
2	20.6	20.5	22.8	23.0	31.9	30.4
3	21.5	20.3	23.4	22.5	31.5	29.3
4	21.3	20.0	23.8	22.3	32.0	32.0
5	21.9	20.4	24.1	23.7	32.1	31.0
Sole	23.1	22.6	24.3	23.7	31.3	31.0
Heel	22.4	22.0	23.3	24.9	31.6	31.0

FIG. 3.—R. B. Thromboangiitis obliterans. Surface temperature after exposure and maximum temperature after tetraethyl ammonium chloride and after nerve block. In the upper extremity after tetraethyl ammonium there was a good rise of temperature but not to the normal level; after nerve block there was a normal level. In the lower extremity after tetraethyl ammonium there was only a slight rise, whereas, after block there were normal levels in all but the left 3d toe which reached 29.3° C. For further details of history and examination, see text.

of tetraethyl ammonium, the maxima reached after peripheral nerve block, the clinical diagnosis and other pertinent case details are shown in Chart I. The range of surface temperatures in each experiment is here indicated by noting the lowest and highest maximum readings among the five digits. The thermocouple readings were corrected by adding or subtracting 0.3° C. for each

degree centigrade that the room temperature was respectively below or above 20° C.

CASE REPORTS

The following two cases show typical results of the experiment:

Case 1.—F. M. (Case 8—Table I) Male diabetic. Age 68. Degenerative arterial disease.

TABLE I

Case No.	Initial	Age	Sex	Diagnosis	Minutes Expos.	Mg. TEAC. I.V.	Extremity	Surface Temp. After Expos. Lowest	Surface Temp. After Expos. Highest	Max. Surface Temp. After TEAC. Lowest	Max. Surface Temp. After TEAC. Highest	Max. Surface Temp. After Block Lowest	Max. Surface Temp. After Block Highest
1	J.S.	23	M	Spastic quadriplegia. No evidence of arterial disease	65	400	RU	21.8	23.2	27.8	28.9	30.0	31.4
					65		LU	21.7	23.3	24.0	26.5	31.5	32.5
					65		RL	18.2	18.7	19.4	20.3	31.2	31.4
					65		LL	18.8	19.6	19.3	20.2	30.8	31.4
2	R.B.	52	M	Thromboangiitis obliterans	50	500	RU	22.3	24.2	28.5	30.3	30.3	31.0
					50		LU	22.0	24.5	27.8	29.4	30.1	31.8
					90		RL	20.6	21.9	22.8	24.1	31.5	32.1
					90		LL	19.9	20.5	22.3	23.7	29.3	32.0
3	M.L.	29	M	Thromboangiitis obliterans	120	300	RU	20.6	21.1	21.5	22.0	30.5	31.8
					120	+	LU	20.1	20.6	20.7	22.0		
					120	200	RL	24.0	25.5	24.3	26.8	24.3	27.3
					120		LL	25.0	27.0	28.3	29.8		
4	G.B.	42	F	Thrombophlebitis. Hypertension. No evidence of arterial disease	35	300	RU	21.2	22.5	28.1	30.9		
					35	+	LU	21.5	23.4	30.1	31.4		
					35	200	RL	22.2	22.6	30.0	30.5		
					35		LL	22.0	22.4	30.1	30.8		
5	M.C.	47	F	Thrombophlebitis. No evidence of arterial disease	63	350	RU	19.0	22.8	20.1	20.8		
					63		LU	19.1	20.3	20.4	21.1		
					63		RL	20.9	21.9	22.8	24.0		
					63		LL	21.7	22.2	25.2	27.0	32.0	*32.8
6	E.M.	49	F	Thrombophlebitic edema. No evidence of arterial disease	120	200	RU	18.9	19.9	22.9	27.4	30.2	31.0
					120	+	LU	18.9	19.9	22.8	23.4	30.8	31.2
					120	300	RL	21.1	21.6	27.8	30.4		
					120		LL	19.5	20.2	27.8	30.7	25.9	*32.0
7	J.R.	61	M	Degenerative arterial disease	45	400	RU	20.3	20.5	22.3	22.5		
					45		LU	20.9	21.7	24.7	25.2		
				Sympathectomized	60		RL	23.3	28.0	24.5	29.0		
					60		LL	25.8	29.6	26.3	30.4		
8	F.M.	68	M	Degenerative arterial disease	135	500	RU	19.9	20.9	20.9	21.0	30.4	30.7
					135		LU	19.9	20.4	20.5	21.0	30.7	30.9
					135		RL	20.8	21.7	21.8	25.3	29.8	30.4
					135		LL	21.2	21.8	23.8	25.3	29.2	30.8
9	G.A.	62	M	Degenerative arterial disease	40	300	RU	21.0	22.5	21.3	22.8	31.0	31.3
					40		LU	21.5	24.0	20.8	23.7	30.0	31.2
					80		RL	19.5	20.0	19.9	20.6	24.0	30.3
					80		LL	20.1	20.5	20.0	20.5	26.6	30.1

Where blocks are indicated, all were on peripheral nerves except the left lower extremity of case No. 5 in which a paravertebral lumbar sympathetic block was done.

* Nerve block incomplete.

Chief Complaint: Pain in arches and toes of both feet. No claudication.

Examination: Right dorsalis pedis pulse +++, left +; both posterior tibial pulses absent. Has elevation ischemia on the left, dependent rubor of both feet, worse on the left. Roentgenograms show marked calcification of arteries of feet and legs.

Figure 1 shows results of exposure, tetraethyl ammonium and nerve block on surface temperatures.

In the upper extremities after tetraethyl ammonium, there were no significant rises, but the temperature after median nerve block reached normal levels.

In the lower extremities after tetraethyl ammonium, there were slight to moderate rises, whereas block produced high sub-maximal temperatures, indicating early vasoconstrictor recession.

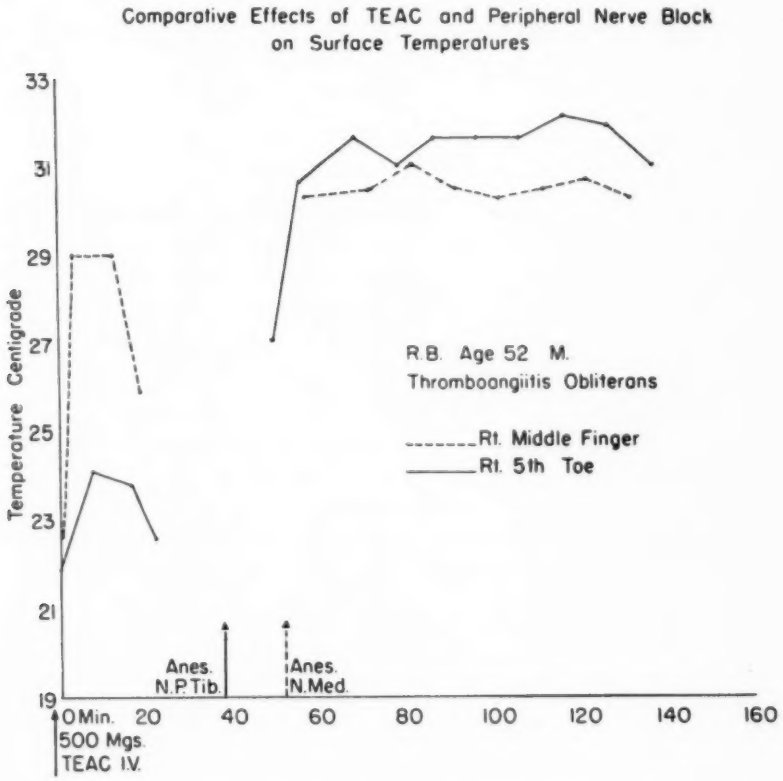

FIG. 4.—Same experiment as Fig. 3. The graph shows the result of the experiment in a single digit in the upper and lower extremities. After tetraethyl ammonium the surface temperature of the finger rose to 29.0° C, the toe to 24.1° C. After nerve block, the finger rose to 31.0° C., the toe to 32.1° C.

If tetraethyl ammonium alone were used, vasoconstrictor recession due to occlusive arterial disease would be diagnosed in all four extremities, advanced in the upper, moderately advanced in the lower extremities. Actually, the vasoconstrictor element was normal in all digits but the left 2nd and 3rd toes where it was submaximal.

Figure 2 shows results of the experiment in a single digit of the upper and lower extremities.

Case 2.—R. B. (Table I) Male. Age 52. Thromboangiitis obliterans.

Chief Complaint: Claudication, right leg, 4 years. No ulceration.

Examination. Right posterior tibial and popliteal pulses 0; all other lower extremity pulses +++. Elevation ischemia + on the right, 0 on the left. Dependent rubor +, both feet. Right radial artery +; left +++. Right ulnar artery +++; left 0.

Figure 3 shows results of exposure, tetraethyl ammonium and nerve block on surface temperature.

In the upper extremities after tetraethyl ammonium, there was a good rise of temperature but not to the normal level. After nerve block a normal level was reached.

In the lower extremities after tetraethyl ammonium, there was only a slight rise, whereas after block there were normal levels in all but the left 3rd toe which reached 29.3° C.

Were tetraethyl ammonium alone used, one would diagnose early vasoconstrictor recession in the upper extremities and advanced vasoconstrictor recession in the lower extremities, whereas the vasoconstrictor element was normal in all digits but the left 3rd toe.

Figure 4 shows the results of the experiment in a single digit of the upper and lower extremities.

SUMMARY OF RESULTS

Intravenous administration of tetraethyl ammonium chloride was followed in certain extremities by a variable rise of surface temperature. In one case (No. 4) tetraethyl ammonium produced a rise of surface temperature to the average normal vasodilatation level in many digits, in other digits to somewhat below this level. No nerve block was done on this patient so that the actual maximum temperature after complete vasomotor paralysis is not definitely known. In all cases in which nerve block was done in addition to the administration of tetraethyl ammonium, any rise of temperature following tetraethyl ammonium was below that proven possible by nerve block. The discrepancy reached 12.2° C. in Case 1; in others, differences of from 8°-10° C. were common. Some digits which had minimal or absent temperature rises following the drug, were proven by nerve block to have the ability to reach or exceed the normal vasodilatation level of 30.5° C. The temperatures of some digits actually fell after tetraethyl ammonium. When a rise of temperature was produced by the drug, the duration of a satisfactory effect was short, averaging about 15 minutes.

CONCLUSIONS

1. The surface temperature effects following the intravenous administration of tetraethyl ammonium chloride were measured under controlled conditions in all 36 extremities in nine patients, eight of whom had various types of peripheral vascular disease. In 21 of these extremities comparison was made with the surface temperature effects of peripheral nerve block; in one with lumbar sympathetic block.

2. The effects of tetraethyl ammonium are variable, undependable, usually incomplete and of short duration.

3. Therefore, tetraethyl ammonium is unsuitable as a diagnostic method in estimating the degree of vasoconstrictor tone in the extremities.

4. These experiments cast doubt on the efficiency of the drug as a vasodilating agent in peripheral vascular disease.

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TETRAETHYL AMMONIUM CHLORIDE— ITS EFFECTS ON SURFACE TEMPERATURES OF ARTERIOSCLEROTIC EXTREMITIES*

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IN THE EARLY YEARS following the discovery of the peripheral vascular effects of paravertebral sympathetic ganglionectomy, the presence or absence of peripheral arterial disease was thought to depend on the degree of vasoconstriction as demonstrated by appropriate tests. We now know that this concept was erroneous and that advanced occlusion may occur in the major peripheral arteries of extremities which still maintain a normal or high vasoconstrictor element. Vasoconstriction is not synonymous with "spasm." It occurs in extremities with normal peripheral vessels, and is also present to a normal or high degree in the early stages of chronic occlusive arterial disease. It is only in the advanced stages of chronic occlusive disease that the vasoconstrictor element has disappeared; all gradations exist between the occlusive disease with normal vasoconstriction and the occlusive disease with vasoconstriction absent.

The degree of vasoconstriction is usually determined by the effect of temporary vasoconstrictor paralysis on the surface temperatures of extremities. This vasoconstrictor paralysis may be produced by general anesthesia, spinal anesthesia, paravertebral sympathetic block, peripheral mixed nerve block or Landis-Gibbon warm water extremity immersion. On the basis of a personal experience with over 400 vasomotor studies over a period of 17 years, the author considers procaine block of the mixed peripheral nerves as the most accurate and reliable.

The reports of the production of "autonomic blockade"[2, 3, 4, 5] by tetraethyl ammonium chloride stimulated the author to compare the results of this drug with vasoconstrictor paralysis produced by methods proven by years of experience to be accurate and dependable, especially by procaine block of mixed peripheral nerves. In a discussion of the article by Coller and his associates[5] on the effects of tetraethyl ammonium, De Bakey[6] reports that local nerve and regional sympathetic block invariably produced increases in skin temperature two to six times greater than that caused by tetraethyl ammonium bromide given intravenously, and that the duration of elevation following block was in every instance considerably more prolonged than the elevation following tetraethyl ammonium. Plethysmography corroborated these results. Later he reported such findings in a normal individual.[7] The author's results on a group

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of subjects suffering from various types of peripheral vascular disease have been reported elsewhere.[8] In that article, the reader will find a full description of the method used in this study.

The present report deals only with the effects of tetraethyl ammonium chloride on 12 cases of degenerative arterial disease, in two of which (Cases 11 and 12) the lower extremities had been previously sympathectomized. The

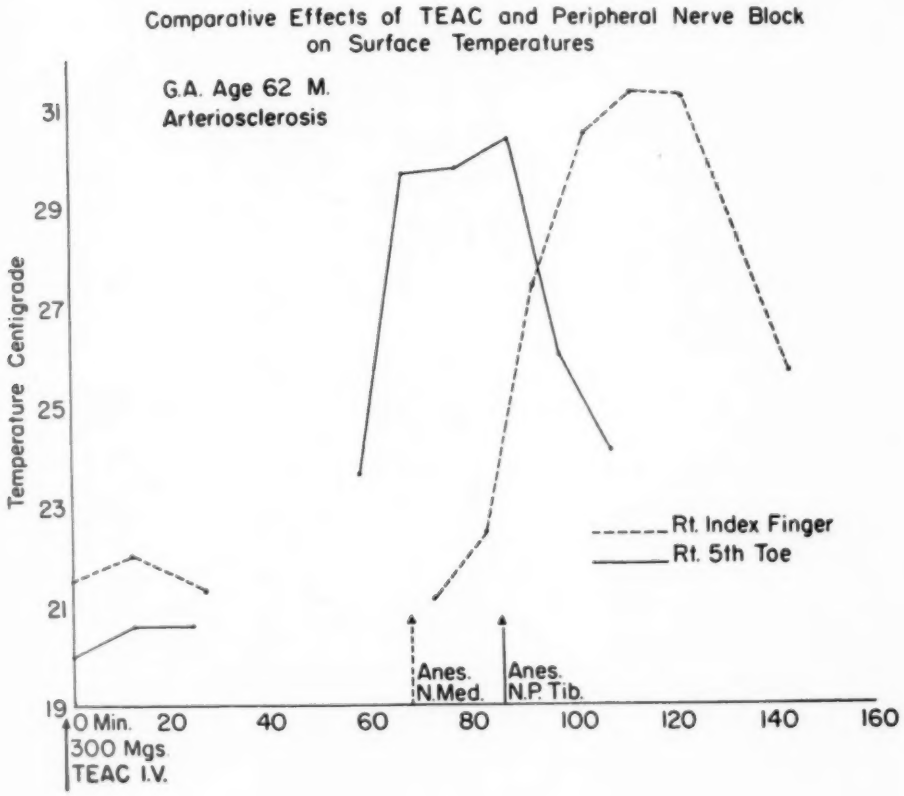

FIG. 1.—Case 3. G. A. Age 62. M.
Claudication of both legs, 2 months, no ulceration or gangrene.
Examination: Dorsalis pedis pulses +++, posterior tibial +, popliteal and femoral pulses +++. No elevation ischemia either side; dependent rubor ++, both sides. Marked trophic disturbances. Marked calcification of foot and leg arteries by x-ray. Mild diabetic.
Neither the finger nor the toe showed any appreciable effect from tetraethyl ammonium. After median and posterior tibial block, both the finger and the toe reached normal vasodilatation level.

important data obtained in this study are set forth in Table I, which gives the dosage of the drug, the surface temperatures of the digits after exposure and the maximum surface temperatures of these digits after tetraethyl ammonium chloride and in most cases after peripheral nerve block. To afford the reader a clearer picture of the results, the lowest and highest maximum temperatures

Comparative Effects of T E A C and Peripheral Nerve Block on Surface Temperatures

G.A. Age 62 M. Arteriosclerosis

Upper Extremities

	After 40" Exposure		Max. After T E A C		Max. After Block	
	R	L	R	L	R	L
Digit 1	22.5	24.0	22.8	23.7	31.0	30.0
2	21.5	23.5	22.0	21.7	31.3	31.2
3	21.0	23.0	21.5	21.4		31.0
4	21.0	22.0	21.5	21.1		
5	21.5	21.5	21.3	20.8		
Palm	25.5	25.5	26.5	26.0		
Dorsum	25.5	26.0	26.1	24.7		
Wrist	26.5	27.0	26.5	27.3		
Midforearm	27.0	28.5	28.3	28.5		
Below Elbow	28.5	28.5	28.0	27.0		
Above Elbow		29.5		30.0		

Lower Extremities

	After 80" Exposure		Max. After T E A C		Max. After Block	
	R	L	R	L	R	L
Digit 1	19.5	20.3	19.9	20.3	24.0	29.8
2	20.0	20.0	20.1	20.0	27.5	26.6
3	20.0	20.5	20.4	20.5	28.2	28.8
4	20.0	20.1	20.6	20.1	28.6	28.1
5	20.0	20.4	20.6	20.4	30.3	30.3
Sole	22.5	21.4	20.0	21.8	29.3	29.2
Heel	22.5	22.1	22.3	22.1	30.0	29.6
Ankle D	23.0	24.0	22.3	24.0		
Midleg	25.0	24.3	24.3	24.3		
Below Knee	26.5	24.0	24.7	24.0		
Above Knee	26.5	25.5	26.5	25.9		

FIG. 2.—Case 3. G. A. Age 62. M.

Upper Extremities: After tetraethyl ammonium there was no significant rise of surface temperature in the digits on the right; an actual fall of surface temperature of the left digits of from 0.3° C. to 1.6° C. After median nerve block there was a normal level in the right 1st and 2nd digits, and in the left 2nd and 3rd digits. The left 1st digit rose to 30° C., slightly under the normal level but within the limits of error of the experiment. The right 3rd digit was not completely anesthetized.

Lower Extremities: After tetraethyl ammonium there was no significant rise of surface temperature on either side. After posterior tibial block there was moderate to good rise on both sides, better on the left, but in no case to the normal dilatation level. The block, however, produced temperature rises varying from 9.9° C. to 4.1° C. higher than that produced by tetraethyl ammonium.

Were tetraethyl ammonium alone used, advanced vasoconstrictor recession would be diagnosed in all four extremities. Actually, the vasoconstrictor response was normal in the upper extremities, moderately decreased in the lower extremities.

of the digits of that particular extremity are noted. In addition, five cases were selected for more detailed description of the effects of tetraethyl ammonium chloride. These represent various stages of development of peripheral arteriosclerosis; in one, the lower extremities had been previously sympathectomized.

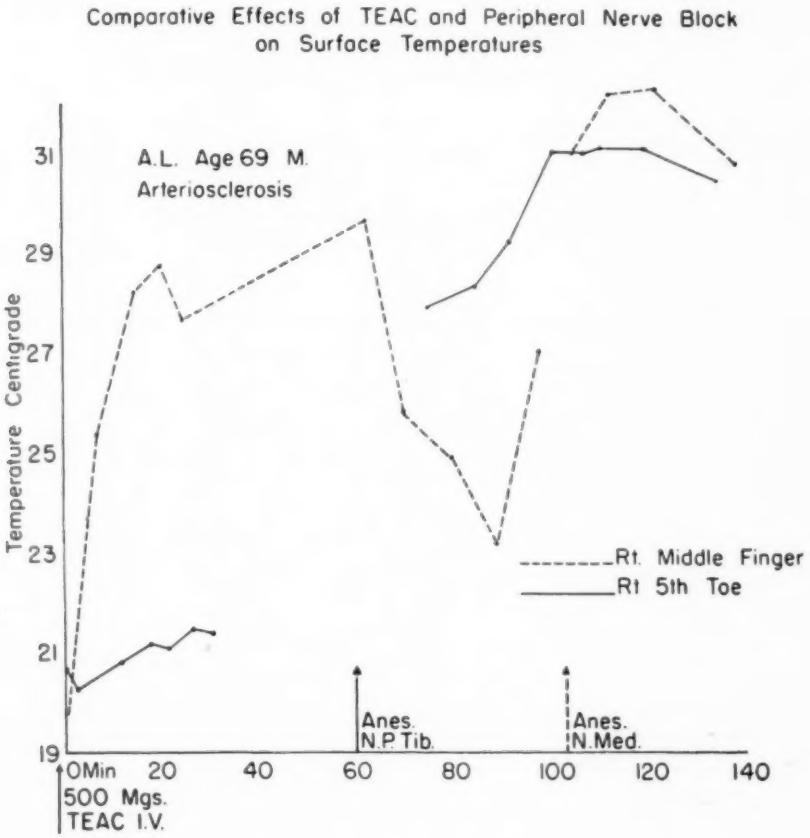

FIG. 3.—Case 4. A. L. Age 69. M.

Claudication of the left calf after walking 1½ blocks; "pins and needles" of left toes and heel for 3 to 4 weeks.

Examination: Femoral pulses +++; all other pulses both sides absent. No elevation ischemia. Dependent rubor + on the left; 0 on the right.

After tetraethyl ammonium chloride there was a marked rise of temperature in the finger, but 3.6° C. below the level reached after block; there was no significant rise of temperature in the toe, yet the temperature after nerve block reached 31.1° C.

These detailed data are reported in a series of figures—a graph and a table for each case. The graphs give a visual impression of the effects of the drug and nerve block on single digits of the extremity. The tables give these data on all the digits of that patient and of the other sites selected for surface temperature measurements.

Comparative Effects of TEAC and Peripheral Nerve Block on Surface Temperatures

A. L. Age 69 M. Arteriosclerosis

Upper Extremities

	After 75" Exposure		Max. After TEAC		Max. After Block	
	R	L	R	L	R	L
Digit 1	20.4	20.9	27.7	23.8	31.1	31.8
2	19.9	20.9	28.2	26.2	32.0	32.1
3	19.8	20.8	28.7	27.7	32.3	32.2
4	19.7	21.2	29.2	28.7		
5	19.8	21.3	29.3	29.3		
Palm	23.3	23.9	29.3	29.7		

Lower Extremities

	After 75" Exposure		Max. After TEAC		Max. After Block	
	R	L	R	L	R	L
Digit 1	21.3	21.8	22.2	22.2	29.9	26.9
2	20.6	22.1	21.7	22.4	30.4	26.7
3	20.7	22.8	21.3	23.6	29.9	26.2
4	20.7	24.8	21.3	25.6	30.5	27.5
5	20.8	25.2	21.2	25.6	31.1	27.3
Sole	24.3	25.3	25.3	28.3	31.3	28.1
Heel	24.0	26.4	24.3	25.7		
Ankle	27.3	27.3				
Midleg	26.9	26.8				
Below Knee	25.8	27.9				
Above Knee	28.3	27.3				

FIG. 4.—Case 4. A. L. Age 69. M.

Upper Extremities: After tetraethyl ammonium chloride there was a good but incomplete rise of surface temperature in most digits. Median nerve block produced normal levels or better in each digit anesthetized.

Lower Extremities: After tetraethyl ammonium chloride there were minimal rises of temperature. After block the temperatures of the right side varied from 29.9° C. to 31.3° C., at or slightly below the normal level; those of the left side varied from 26.2° C. to 28.1° C., showing evidence of moderately advanced recession of vasoconstriction due to occlusive arterial disease.

If tetraethyl ammonium chloride alone were used the normal response in the upper extremities would be overlooked; the right lower extremity would have been judged to have advanced arterial disease without vasoconstriction, whereas there was a submaximal vasoconstrictor element still present; and in the left lower extremity, the rise to a moderate range would have been missed. In both lower extremities sympathectomy would probably have been denied the patient, whereas block indicates without question that following sympathectomy a marked increase in temperature would follow on the right and a moderate increase on the left.

SUMMARY

Tetraethyl ammonium chloride was given intravenously to 12 patients all of whom were suffering from peripheral arteriosclerosis; the lower extremities of two of these (Cases 11 and 12) had been previously sympathectomized. The effect of tetraethyl ammonium chloride on the surface temperatures was measured in all 46 extremities; in 31 of these surface temperatures were also

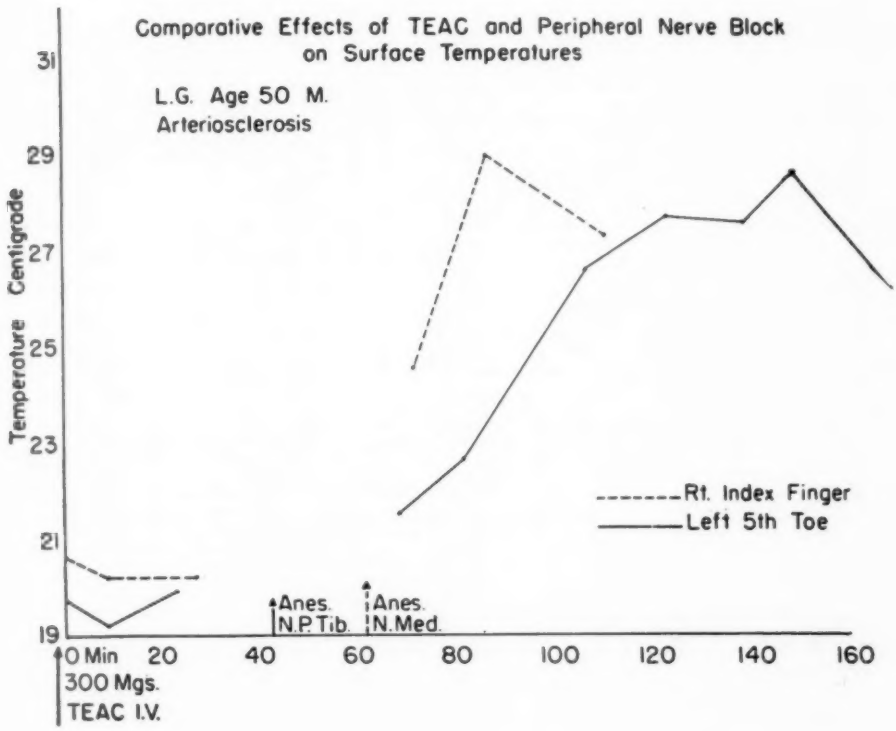

FIG. 5.—Case 5. L. G. Age 50. M.
Mild diabetic. Claudication both legs after walking 1½ level blocks, 4 months.
Examination: All pulses +++. Angiospastic claudication.
After tetraethyl ammonium chloride no rise of temperature in finger or toe. After block, finger temperature rose to 28.9° C., the toe to 28.5° C. Mild vasoconstrictor recession in finger and toe. Other digits had more recession. (See table, Fig. 6).

measured after vasoconstrictor paralysis was produced by procaine block of mixed peripheral nerves, in two by subarachnoid block.

Tetraethyl ammonium chloride produced significant rises in surface temperature to 26° C. or over in only three of 42 extremities (excluding the sympathectomized extremities). Rise of temperature to 26° C. or over was obtained in 25 of the 32 extremities subjected to procaine block; rises to 28° C. or over in 20 of these extremities; and rises to 30° C. or over in 14 of these

TABLE I.—*Summary—All Cases*

Case No.	Initial	Age	Sex	Mg. Teac. I.V.	Extremity	Surface Temperature After Exposure		Maximum Surface Temperature After Teac.		Maximum Surface Temperature After Block	
						Lowest	Highest	Lowest	Highest	Lowest	Highest
1	F.Z.	52	M	500	Right upper	19.1	19.4	20.3	20.7		
					Left upper	19.1	20.1	19.9	20.4		
					Right lower	19.9	20.5	21.6	26.3	30.2	31.5
					Left lower	20.1	20.6	21.3	25.5	31.5	32.0
2	F.M.	68	M	500	Right upper	19.9	20.9	20.9	21.0	30.4	30.7
					Left upper	19.9	20.4	20.5	21.0	30.7	30.9
					Right lower	20.8	21.7	21.8	25.3	29.8	30.4
					Left lower	21.2	21.8	23.8	25.3	29.2	30.8
3	G.A.	62	M	300	Right upper	21.0	22.5	21.3	22.8	31.0	31.3
					Left upper	21.5	24.0	20.8	23.7	30.0	31.2
					Right lower	19.5	20.0	19.9	20.6	24.0	30.3
					Left lower	20.0	20.5	20.0	20.5	26.6	30.3
4	A.L.	69	M	500	Right upper	19.7	20.4	27.7	29.3	31.1	32.3
					Left upper	20.8	21.3	23.8	29.3	31.8	32.2
					Right lower	20.6	21.3	21.2	22.2	29.9	31.1
					Left lower	21.1	25.2	22.2	25.6	26.2	27.5
5	L.G.	50	M	300	Right upper	20.5	21.5	20.2	21.2	28.7	28.9
					Left upper	19.8	20.5	19.9	20.9	28.7	29.1*
					Right lower	19.4	19.6	19.2	19.5	21.8	26.8
					Left lower	19.5	19.7	19.8	20.0	26.6	28.7
6	N.A.	58	F	500	Right upper	21.0	21.4	21.7	22.3	27.7	28.5
					Left upper	21.2	21.9	21.8	22.5	28.5	28.6
					Right lower	22.9	24.2	23.8	24.8	25.0	26.0
					Left lower	22.6	22.8	22.5	23.0	23.5	24.5
7	C.R.	62	M	500	Right upper	21.2	21.6	22.7	25.6		
					Left upper	21.2	22.2	21.2	22.4	28.8	30.2
					Right lower	22.6	26.1	21.9	24.6	22.4	23.8
					Left lower	23.4	24.1	21.4	22.4	21.7	24.2
8	D.L.	55	M	500	Right upper	20.0	22.0	21.0	21.7	25.0	27.2
					Left upper	20.0	21.2	21.1	23.1	27.9	29.5
					Right lower	20.3	21.0	21.2	21.7	21.0	21.4
					Left lower	20.5	21.0	21.0	21.5	20.8	26.5
9	L.R.	65	M	300 + 200	Right upper	20.0	21.5	21.0	24.1		
					Left upper	20.5	22.0	21.2	23.2		
					Right lower	23.1	23.6	23.3	23.7	22.1†	22.4†
					Left lower	20.6	21.1	20.4	22.1	21.9†	24.0†
10	M.T.‡	56	M	200	Right upper	20.4	21.4	20.6	21.6	21.1*	21.6*
					Left upper	19.9	20.4	20.5	20.7	21.0	22.3
11	H.N.	64	M	410	Right upper	21.6	22.8	21.7	22.0		
					Left upper	22.1	22.7	20.8	21.4		
					Right lower**	27.6	30.0	24.6	29.5		
					Left lower**	23.3	28.9	23.1*	28.5*		
12	J.R.	61	M	400	Right upper	20.3	20.5	22.3	23.2		
					Left upper	20.9	21.7	24.7	25.2		
					Right lower**	23.3	28.0	24.5	29.0		
					Left lower**	25.8	29.6	26.3	30.4		

* Temperature still rising very slowly.
** Sympathectomized.
† Subarachnoid block.
‡ Both legs amputated for arteriosclerotic gangrene.

Comparative Effects of TEAC and Peripheral Nerve Block on Surface Temperatures

L. G. Age 50 M. Arteriosclerosis

Upper Extremities

	After 90" Exposure		Max. After TEAC		Max. After Block	
	R	L	R	L	R	L
Digit 1	21.5	20.5	21.2	20.9	28.7	29.1*
2	20.6	20.0	20.2	20.2	28.9	29.9*
3	20.6	20.0	20.4	20.1	28.7	28.7*
4	20.6	19.9	20.5	20.0		
5	20.5	19.8	20.4	19.9		
Palm	25.0	24.0	23.8	23.2		
Dorsum	24.6	23.6	23.1	23.0		
Wrist	26.0	26.4	25.1	24.7		
Midforearm	28.8	28.2	28.1	28.0		
Below Elbow	29.5	29.4	29.1	29.6		

Lower Extremities

	After 90" Exposure		Max. After TEAC		Max. After Block	
	R	L	R	L	R	L
Digit 1	19.6	19.7	19.4	20.0	21.8	27.1
2	19.5	19.6	19.3	19.9	23.3	26.6
3	19.4	19.5	19.2	19.9*	25.1	27.1
4	19.5	19.5	19.2	19.8*	25.2	27.0
5	19.5	19.7	19.5	19.9*	26.8	28.7
Sole	22.2	22.3	21.2	21.5	25.4	27.5
Heel	21.4	21.8	21.4	21.5	26.8	27.8
Ankle	23.7	23.7	22.6	23.6		
Midleg	25.7	24.7	24.7	24.0		
Below Knee	25.2	24.2	25.2	24.5		
Above Knee	26.5	27.1	26.2	25.9		

FIG. 6.—Case 5. L. G. Age 50. M.

After tetraethyl ammonium chloride there were no significant rises of temperature in any of the 4 extremities.

After block, the upper extremity digits rose to from 28.7° C. to 29.1° C., indicating a mild vasoconstrictor recession. The lower extremity digits rose only to from 21.7° C. to 25.2° C. on the right, and from 26.6° C. to 27.1° C. on the left, indicating a moderate to severe vasoconstrictor recession due to occlusive arterial disease.

If tetraethyl ammonium alone were used a high subnormal vasoconstrictor element would have been overlooked in the upper extremities and a moderate vasoconstrictor element would have been overlooked in the left lower extremity.

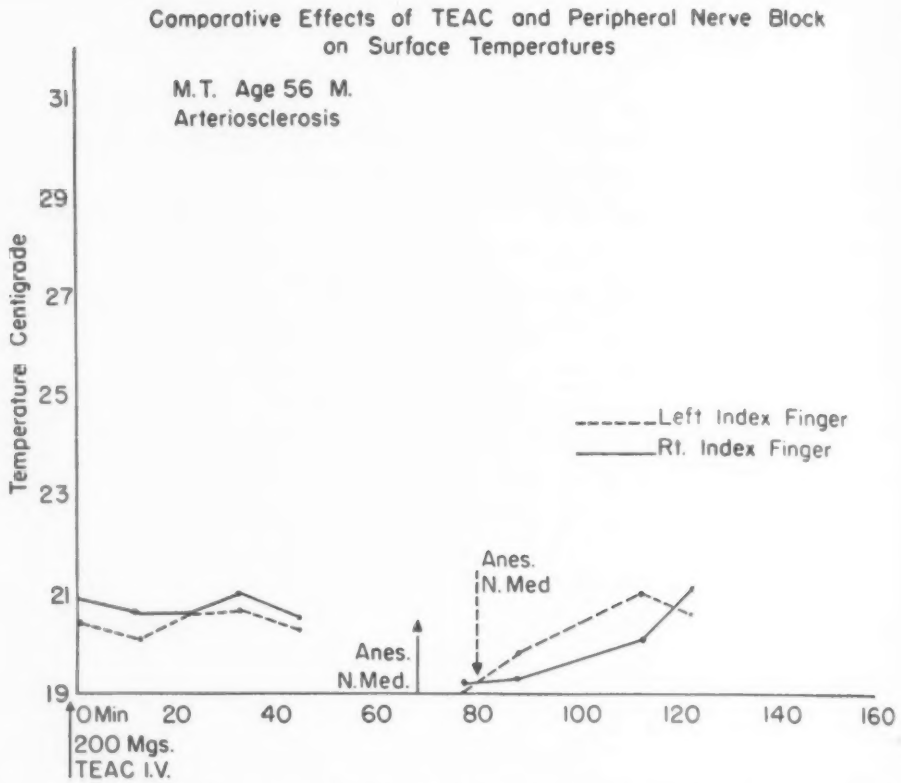

FIG. 7.—Case 10. M. T. Age 56. M. Extensive general and peripheral sclerosis. Amputations through both low thighs for arteriosclerotic gangrene in 1939 and 1941. *Examination:* Gangrene of the right ring and left middle fingers, 4 months. Marked cyanosis and pallor of both hands. Both brachial pulses +++, radials and ulnars not felt. X-rays show mild calcification of the right subclavian artery; none in the hands, forearms or arms. Old valvular heart disease. Surface temperatures both after tetraethyl ammonium chloride and after block show practical absence of vasoconstrictor tone.

Comparative Effects of TEAC and Peripheal Nerve Block
on Surface Temperatures

M.T. Age 56 M. Arteriosclerosis

Upper Extremities

	After 70" Exposure		Max. After TEAC		Max. After Block	
	R	L	R	L	R	L
Digit 1	21.4	20.4	21.6	20.7	22.1*	22.3
2	20.9	20.4	21.0	20.7	21.1 *	21.0
3	20.4	20.4	21.0	20.6	21.6*	21.1
4	20.4	19.9	21.1	20.6		
5	20.4	19.9	20.6	20.5		
Palm	24.4	24.9	23.7	24.3		
Dorsum	22.9	24.4	23.6	23.8		
Wrist	25.4	24.9	25.0	25.0		
Midforearm	27.9	26.9	27.5	26.8		
Below Elbow	28.9	27.9	28.6	28.0		
Above Elbow	29.9	29.4	29.4	28.9		

FIG. 8.—Case 10. M. T. Age 56. M. Neither tetraethyl ammonium chloride nor block produced significant rises of temperature. The vasoconstrictor element has practically completely disappeared. On the right side, after block, readings were discontinued before actual maxima were reached. The slow rise after 35 minutes, however, indicates that the figures are close to the maxima. Although tetraethyl ammonium and block produced the same results, no rise of temperature was possible and the similarity of responses is no proof of the dependability of tetraethyl ammonium chloride.

extremities. In all three of the extremities which showed rises to 26° C. or over by tetraethyl ammonium chloride, nerve block produced a rise of temperature above the normal level of 30.5° C. In the sympathectomized extremities the drug was followed by a change of from —1.7° C. to +1.2° C. When vasodilatation occurs as the result of tetraethyl ammonium chloride, the average duration of a satisfactory effect (25° C. or over) is 15 minutes.

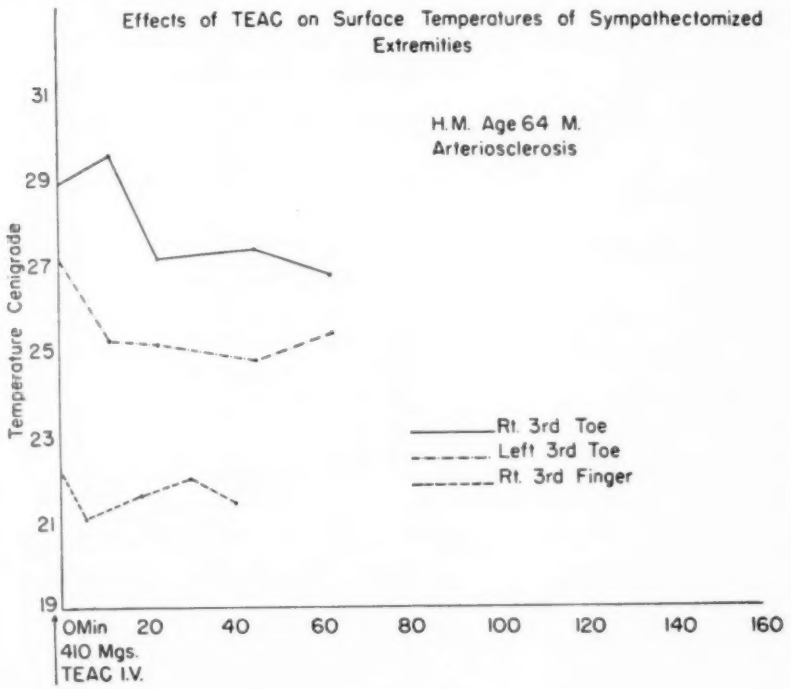

FIG. 9.—Case 11. H. M. Age 64. M.

Claudication of both calves after walking two blocks since October, 1944; night pain in the soles since November, 1944.

Examination: Femoral pulses ++, all others 0. Bilateral marked elevation ischemia, slight dependent rubor. Moderate vasoconstrictor element. Bilateral lumbar ganglionectomy, March, 1945.

After tetraethyl ammonium chloride, the right toe showed a 0.6° C. rise of temperature; the left showed a 1.7° C. fall of temperature. 0.6° C. is within the limit of error in the experiment. The finger showed no significant change.

CONCLUSIONS

1. Comparison of tetraethyl ammonium chloride given intravenously, and of vasoconstrictor paralysis produced by peripheral nerve procaine block, shows that tetraethyl ammonium chloride is undependable and unsatisfactory as a diagnostic agent in estimating the vasoconstrictor element in extremities affected by peripheral arteriosclerosis.

2. In peripheral arteriosclerosis vasodilatation due to tetraethyl ammonium chloride is infrequent; when it occurs it is only partial and its duration is short.

3. These experiments throw grave doubt on the value of tetraethyl ammonium chloride as a practical therapeutic agent in peripheral arteriosclerosis.

Effect of TEAC on Surface Temperatures of Sympathectomized Extremities

H.M. Age 64 M. Arteriosclerosis

Upper Extremities (not Sympathectomized)

	After 115" Exposure		Max. After TEAC		
	R	L	R	L	
Digit 1	22.8	22.4	21.9	21.2	
2	22.6	22.3	22.0	21.1	
3	22.1	22.4	22.0	208	
4	21.9	22.1	21.7	21.3	
5	21.6	22.7	21.8	21.4	
Palm	24.3	24.6	24.1	23.7	
Dorsum	24.4	25.7	23.1	22.5	
Wrist	26.1	26.1	25.4	25.0	
Midforearm	28.1	28.4	28.1	27.6	
Below Elbow	29.9	29.6	29.4	28.7	
Above Elbow	29.1	29.1		28.7	

Lower Extremities (Sympathectomized)

	After 115" Exposure		Max. After TEAC		Effect of TEAC	
	R	L	R	L	R	L
Digit 1	27.6	28.5	28.2	28.5*	+0.6	0
2	29.1	28.9	29.2	28.5*	+0.1	−0.4
3	28.9	27.0	29.5	25.3	+0.6	−1.7
4	24.0	23.3	24.6	23.1*	+0.6	−0.2
5	30.0	27.5	28.9	26.2	−1.1	−1.3
Sole	28.5	28.6	27.3	27.7	−1.2	−0.9
Heel	30.1	29.0	28.5	29.6	−1.6	+0.6
Ankle	29.3	30.6	29.2	29.6	−0.1	−1.0
Midleg	28.3	28.0	27.2	27.2	−1.1	−0.8
Below Knee	28.6	26.6	26.6	26.2	−2.0	−0.4
Above Knee	29.1	29.6	31.0	31.0	+1.9	+1.4

FIG. 10.—Case 11. H. M. Age 64. M.

Upper Extremities: (Not sympathectomized). After tetraethyl ammonium chloride there was no significant change in surface temperature. In fact, all but the right 5th digit showed an actual fall of temperature.

Lower Extremities: (Sympathectomized) After tetraethyl ammonium chloride there were changes in surface temperature varying on the right from −2.0° C. to +1.9° C. and on the left from −1.7° C. to +1.4° C. These changes are not significant. In the digits the rise on the right was not more than 0.6° C.; on the left there was a fall in four digits.

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CHRONIC PROGRESSIVE INFECTIOUS GANGRENE OF THE SKIN*

A PATIENT WITH EXPOSURE TO COLD WAVE SOLUTION

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CHRONIC INFECTIOUS GANGRENE of the skin is an uncommon disease. Meleney[1] distinguished four varieties: Postoperative progressive bacterial synergistic gangrene, gangrenous impetigo; fusospirochetal gangrene; and amebic infection with gangrene. Occasional cases are seen which do not fit any of these chronic categories. They do not conform with the characteristic pictures of the acute infectious gangrenous lesions of the skin, and they differ in their natural history from the ordinary pyogenic infections of the skin and subcutaneous tissues.

The course of an infection is determined by the virulence of the bacteria, by the nature of the tissue to which they have gained access, and by the ability of the patient's natural defenses to cope with the infection. The individual's inherent ability to combat infection can be modified by a number of different factors, among them, exposure to injurious chemical agents. Exposure to benzol, for instance, causes a leukopenia and renders the patient peculiarly susceptible to infections of the skin and other organs. The patient to be described had an unusual type of chronic progressive gangrene of the skin of the abdominal wall. Her defense reaction was peculiar in that a leukopenia, rather than a leukocytosis, accompanied the infection. Recently, Cotter[2] reported five patients (Table V) who showed skin and systemic manifestations which he attributed to the toxic effects of thioglycolic acid in "cold wave" hairdressing solutions. The patient to be described, a hairdresser, is therefore of particular interest because in addition to the problem of management of a serious surgical lesion, she raises the question of the rôle that exposure to thioglycolic acid or thioglycolates in "cold wave" solutions may have played in her peculiar susceptibility to infection.

CASE REPORT

The patient was a 33-year-old single hairdresser. In 1934 she had been operated upon for acute appendicitis. The convalescence was complicated by the development of pelvic and perirenal abscesses which required drainage. That same year she was operated upon for symptoms of intestinal obstruction. Bilateral salpingectomy and right oophorectomy were done. Most of the left ovary was also removed for "cystic oöphoritis." She recovered satisfactorily from these operations and had always to watch her diet for fear of gaining weight.

* Submitted for publication, February 1948.

The patient worked as a hairdresser for 11½ years in addition to attendance at a hairdressing school for 2 years. For 9 years she had worked in a very active beauty parlor establishment of her own. Since March, 1944, she had been waving hair by the "Cold Wave" method. She worked long hours, often up to 10 or 12 hours a day and administered personally 6 to 12 "cold-wave" treatments a month. She developed no rashes or other obvious signs of toxicity, however, except that her finger tips would become very sore after applying cold wave solutions. She kept on working until her present acute illness.

During the past 2 years she had shown signs of unusual susceptibility to infection. In June, 1945, she was stung by a mosquito on the medial aspect of the right ankle. The lesion became secondarily infected, she was febrile and acutely ill for several days. The lesion took 6 weeks to heal and a brown spot is still visible at the site of the lesion. In January, 1946, she bumped the lateral aspect of her ankle against a rocking chair. There was no obvious break in the skin but an abscess developed there. It had to be "lanced" twice, sulfonamides were administered, and the lesion required 4 weeks to heal. The site of this lesion, too, is still marked by the presence of an area of brown pigmentation.

For 3 months before the onset of her present acute illness, she had begun to complain of easy fatiguability. She had noticed a small external hemorrhoidal tab during that time, but it had caused no inconvenience until April 21, 1947, when she noticed that the hemorrhoid had suddenly increased in size. She felt feverish and was too ill to leave her house. Her family physician was called to see her and for the next 3 days she was treated with bedrest and oral penicillin. She took 400,000 units a day in the form of tablets (50,000 units each). No sulfonamides were administered. She failed to improve and she was admitted to the Jane Brown Memorial Unit of the Rhode Island Hospital on April 24, 1947,* where penicillin therapy was continued and, in addition, sulfadiazine (1 Gm. every 4 hours orally) was started. Examination of the blood on admission, before any therapy had been started, revealed only 6000 white blood cells per cubic millimeter with 78 per cent polymorphonuclear cells and 21 per cent lymphocytes. A leukocytosis had been anticipated and, because of its absence, the sulfadiazine was discontinued for fear of aggravating a leukopenia.

Upon admission to the hospital, physical examination had revealed a large gangrenous external hemorrhoid and a blister-like pustule on the lower third of her left leg. This contained thin cloudy fluid. Nothing grew from it on culture. Subsequently, she developed a similar blister in the lower end of a broad right paramedian lower abdominal scar. Both blisters broke spontaneously. The one on the shin healed; that in the abdominal scar left an ulceration which spread progressively, instead of healing, until the surface of the entire scar had "melted away."

The oral temperature on admission was 104° Fahrenheit. During her hospital stay the temperature varied between 102 and 104 orally. The thrombosed hemorrhoid gradually separated and by the end of 3 weeks it was no longer present. Her general condition continued to fail, however. The lateral abdominal scar also became ulcerated and induration developed in the skin between the scars. She had severe night sweats and continued to lose weight. An exploratory laparotomy under ether anesthesia and through a subcostal incision was done on May 21, 1947. Abdominal Hodgkins disease or a liver abscess had been suspected. Neither was found. The wound healed well and the operation appeared to have had no adverse effect. She lost 23 pounds in weight during the first 5 weeks of hospitalization.

Among the numerous laboratory examinations done (Tables I and II) only 2 were of positive interest, namely, the increased sedimentation rate and the leukopenia without agranulocytosis.

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* The writers are indebted to Dr. William P. D'Ugo and to Dr. Daniel V. Troppoli for much of the information relative to this hospital admission.

On May 29, 1947, she was transferred from the Jane Brown Memorial Unit of the Rhode Island Hospital to the Baker Memorial division of the Massachusetts General Hospital. She appeared critically ill and had an oral temperature of 101 degrees Fahrenheit with a pulse rate of 120 beats per minute. Her blood pressure was 120 millimeters of mercury systolic and 68 diastolic, but her skin was cold and clammy. Except for the general systemic reaction, the positive findings were confined essentially to the right lower quadrant of the abdomen. Here there were 2 operative scars, a paramedian one and an

TABLE I.—*Blood Cytology from Records of Jane Brown Memorial Unit of the Rhode Island Hospital*

Date (1947)	Red Blood Cells Per Cubic Millimeter of Blood	Hemoglobin (Gm. Per Cent)	White Blood Cells Per Cubic Millimeter of Blood	Differential Count (As Per Cent of Total White Blood Cells)				
				Polymorphonuclear Cells	Lymphocytes	Monocytes	Basophiles	Eosinophiles
24 April	2,640,000	....	6,000	79	21	..	..	..
26 April	.....	....	6,200	71	27	1	..	..
28 April	.....	....	7,850	57	42	1	..	..
30 April	3,690,000	10.8	4,550	66	32	2	..	..
3 May	.....	....	3,750	61	37	2	..	..
5 May	.....	....	2,900	57	43	..	..	..
10 May	.....	....	2,550	62	38	..	..	..
11 May	.....	....	1,750	..	..	..	..	..
14 May	.....	....	4,600	59	41	..	..	..
22 May	3,890,000	11.2	3,650	77	23	..	..	..
26 May	.....	....	9,350	80	17	1	..	..

TABLE II.—*Additional Laboratory Data from Records of Jane Brown Memorial Unit of the Rhode Island Hospital.*

Date (1947)	Examination	Result	Other Tests Performed (April–May 1947)	
			Examination	Result
25 April	Hinton	Negative	Typhoid-dysentery agglutinations	Negative
1 May	Hinton	Negative	Heterophile antigen (5 tests)	Negative
24 April	Blood culture	Sterile	Skin tests and opsonocytophagic test for brucellosis	Negative
30 April	Blood culture	Sterile	Tuberculin test 1:1000	Negative
16 May	Blood culture	Sterile	Frei test	Negative
17 May	Blood culture	Sterile	Roentgenogram of chest	Negative
			Plain roentgenogram of abdomen	Negative
			Sedimentation rate (4 tests)	All elevated to 3 times normal
			Icteric index	Normal
			Stools	Negative for ova, parasites and blood
			Smears for malaria (2 tests)	Negative
			Excretion of phenolsulfonphthalein	Normal
			Urinalysis and culture of urine	Negative

oblique one more laterally (Fig. 1). Both were now open ulcerations throughout most of their extents since the covering epithelium had undergone a dissolution. There was no undermining of the skin. Around and between the two lower abdominal ulcerated scars the skin was indurated and edematous. Nodular elevations about 0.5 cm. in diameter in the skin suggested multiple abscesses but there was no fluctuation. Immediately around the outer of the two scars, and extending mostly laterally from it was an irregular swell-

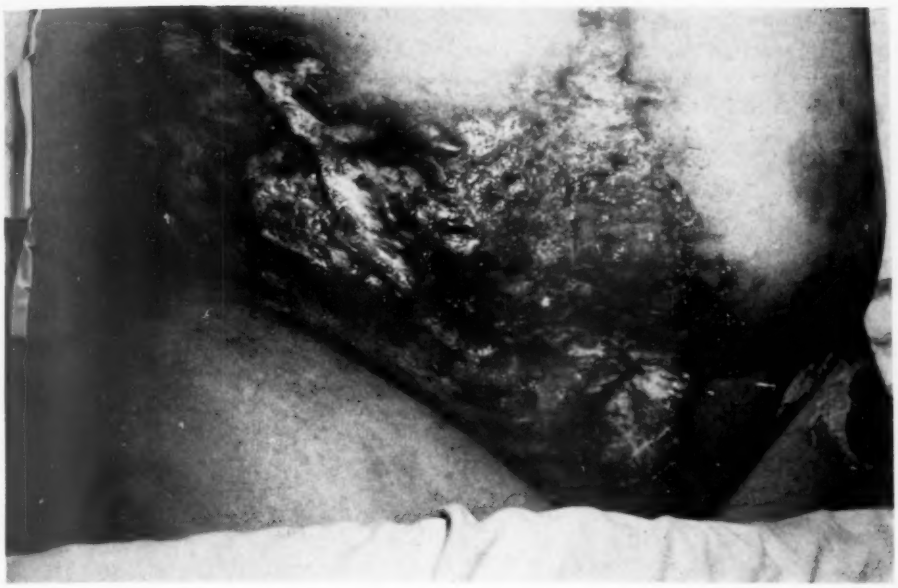

FIG. 1.—Photograph of lesion of abdominal wall before operation. Note the dissolution of epithelium over the scars from previous operations, the margin of cellulitis extending from the lesion particularly upward and to the right, and the granulomatous appearance of the lesion with blister formation.

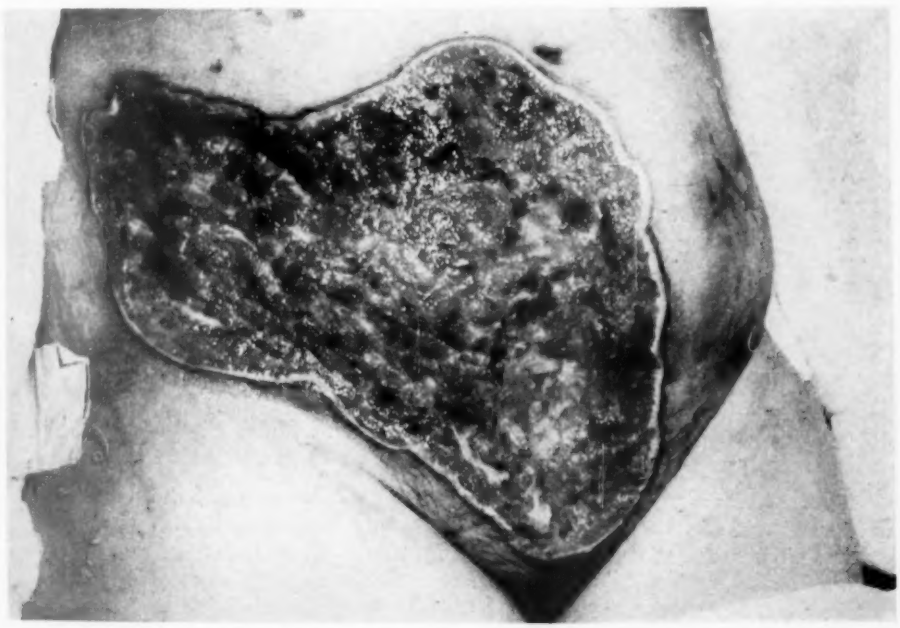

FIG. 2.—Photograph taken on June 21, 1947, at the time of the second dressing to show the extent of the excision. The area is granulating well and some of the Thiersch grafts have taken.

ing measuring 6 by 9 centimeters. The swelling was nodular. The nodules measured 0.5 to 1.0 cm. in diameter and some were ulcerated. No pus could be obtained from any of the ulcerated nodules. A culture from one of the ulcerated areas showed *E. coli*, *Staphylococcus aureus* and alpha-hemolytic Streptococci. Cultures for fungi were negative. On the inferior lateral surface of the granulomatous tumor, the surface epithelium was raised as a bleb by cloudy fluid. This fluid was examined for fungi and yeasts but none was found. The smear did show many polymorphonuclear cells and a few gram-positive cocci. During 5 days of observation, the granulomatous lesion increased in size, extending

TABLE III.—*Blood Cytology from Records of Massachusetts General Hospital.*

Date (1947)	Hemoglobin (Gm. Per Cent)	White Blood Cells Per Cubic Millimeter of Blood	Polymorphonuclear Cells	Differential Count (As Per Cent of Total White Blood Cells)					
				Large Lymphocytes	Small Lymphocytes	Monocytes	Basophiles	Eosinophiles	Platelets
29 May	10.7	7,700	74	..	24	2	..	..	Slighty increased
3 June	....	6,400							
4 June*	12.0	4,200	86	..	11	1	..	1	Slightly increased
5 June	....	2,700							
5 June	....	3,300	54	3	40	3	..	..	Slightly increased
6 June	....	4,300	64	1	32	1	..	2	Normal
7 June	....	5,000	62	2	30	5	..	1	Normal
9 June	13.4	6,700	75	..	22	3	..	..	Normal
10 June	12.6	9,800	87	..	10	1	..	2	Normal
11 June	12.6	6,000	72	2	20	6	..	..	Normal
12 June	11.4	6,600	73	..	24	2	..	1	Normal
13 June	....	5,800	63	..	32	4	..	1	Normal
14 June**	....	3,800	75	..	20	2	..	2	Slightly increased
16 June	....	4,700	61	..	32	5	..	2	Slightly increased
18 June	12.2	4,000	50	..	47	3	..	..	Norma.
19 June	....	5,400	53	5	35	5	1	1	Slightly increased
20 June	11.8	4,600	54	..	40	6	..	..	Slightly increased
21 June	12.6	5,400	49	11	38	..	..	2	Slightly increased
23 June	....	6,700	78	..	18	2	..	2	Slightly increased
24 June	....	3,900	52	1	44	2	..	1	Increased
25 June	....	6,900	71	..	27	..	..	2	Increased
26 June	....	5,600	69	..	30	1	..	..	Slightly increased
27 June	....	6,400	63	..	33	3	..	1	Increased
28 June	....	5,600	55	2	41	2	..	..	Normal
30 June	10.7	6,300	58	..	38	2	..	2	Slightly increased
8 July	10.2	3,400							
11 July**	....	7,300	41	4	52	..	..	2	Normal
12 July	....	....	61	1	34	3	..	1	Normal
15 July	12.2	7,500	58	..	38	1	..	3	Normal
21 July	12.2	7,400	53	1	43	2	..	1	Normal
1 August***	11.8	6,800	49	..	46	2	1	2	Normal

* One per cent of cells in this smear unclassified.
** One "blast" form seen in white cell differential in this smear.
*** At this examination, the red blood cell count was 3.84 million; the hematocrit was 40%.

laterally for the most part and the ulceration on the paramedian scar spread in all directions. It extended onto the pubis to 1 centimeter from the vulva. The entire involved area was circumscribed in the right lower quadrant of the abdomen by a one-half inch margin of bluish-purple discoloration (Fig. 1).

The admission white blood cell count was 7,700 per cubic millimeter of blood with 74 per cent polymorphonuclear cells. The hemoglobin concentration was 10.7 Gm. per cent. This rose to 12.0 Gm. per cent after the transfusion of 1500 cc. of citrated blood. The blood cytology throughout her hospital stay was characterized by a variable degree of

leukopenia, a normal or slightly augmented proportion of platelets in the smear, and occasionally a relative lymphocytosis (Table III). Examinations of the urine showed only a few white blood cells in the centrifuged specimens and 1+ albumen which was not found in a catheter specimen. Examinations of the stool on 5 occasions were negative for blood, parasites and ova. One specimen was cultured and no pathogens were found. The heterophile antigen test was negative and agglutination tests for brucellosis* and for the typhoid-dysentery group were negative. Two blood cultures were negative. The patient's blood was Rh positive and belonged to Group O. Other tests that were done are recorded in Table IV.

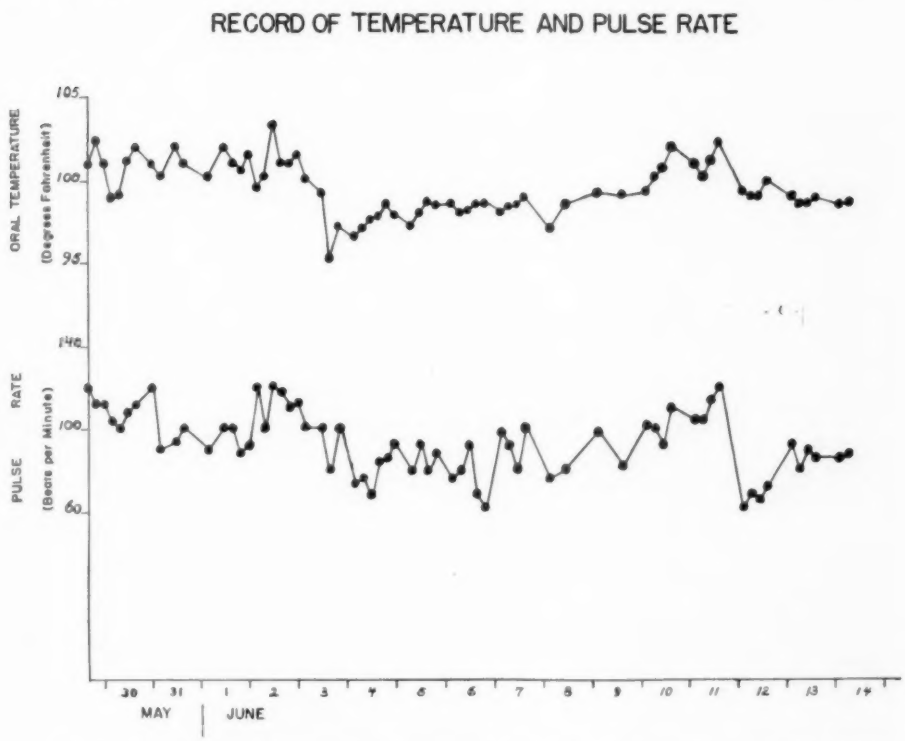

FIG. 3.—A chart of the patient's temperature and pulse rate before and after excision of the lesion on June 3, 1947. Note the drop of the temperature to subnormal levels for the day of operation and for the next day.

On June 3, 1947, a block-excision of the involved skin of the right lower quadrant was done by diathermy under ether anesthesia. The excision was carried through the subcutaneous tissue and onto the deep fascia which did not appear involved. The circumference of the excision was carried beyond the band of bluish-purple discoloration (Fig. 2). The inflammatory process included multiple small areas of necrosis in the subcutaneous tissue. There was no gross evidence of actinomycosis and cultures from the necrotic areas showed non-hemolytic *Staphylococcus aureus* and alpha-hemolytic Streptococcus. Anaerobic cultures showed no growth. The Staphylococcus grew in a medium containing 0.3 units of penicillin per cc., but was inhibited by 0.6 units per cc. The Streptococcus grew even when the medium contained as much as 5 units of penicillin per cc.

* Opsonocytophagic index and skin tests for brucellosis were done at the Jane Brown Memorial Unit of the Rhode Island Hospital and were negative.

The effect of the excision of the lesion upon the patient's temperature was remarkable (Fig. 3). Beginning six days after the excision and twice again during the next month, "postage-stamp" split-thickness skin grafts from the thighs were applied to the granulating surface until it was almost completely covered. There was a temperature reaction after the first graft, but none after the others. A specimen of sternal marrow was taken for biopsy on July 31, 1947. Supra vital stains of impressions from the marrow as well as histologic sections of it showed scant marrow with no diagnostic abnormality. (Since this paper was written the patient has been hospitalized again because of severe anemia and leukopenia following an upper respiratory infection and a paronychia. At this admission, blood smears showed severe depression of the platelet count and two bone marrow aspirations showed "insufficient tissue for diagnosis" and "fibrosis of bone marrow" respectively.)

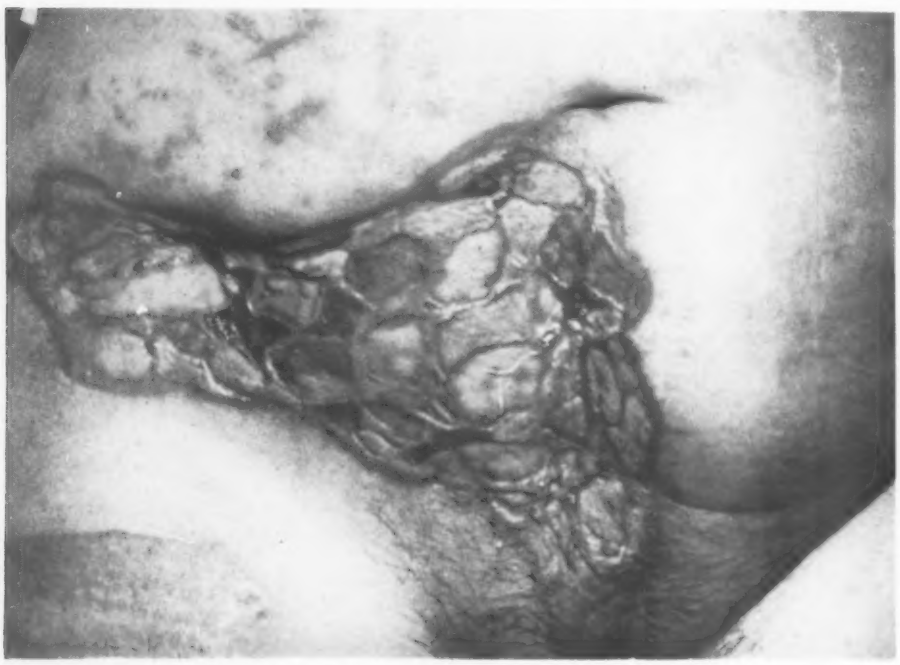

FIG. 4.—Appearance of grafted area on July 30, 1947, eight weeks after excision of the lesion.

She did very well after excision of the infected skin. The grafts grew satisfactorily and by the time she left the hospital, the area had epithelialized almost completely (Fig. 4). On the day of discharge, August 2, 1947, she weighed 140.5 pounds.

Follow-Up Notes

October 21, 1947: The patient has gained weight so that she now weighs 152 pounds in her dress and shoes. The right lower quadrant of the abdomen is completely epithelialized (Fig. 5) and depressions in the grafted area are filling out. The concentration of plasma proteins is 6.0 grams per cent. The hematocrit is 36 per cent (hemoglobin 12.2 Gm. per cent). A count of the white blood cells was not done. She was encouraged to lose weight and a well balanced low-caloric diet was prescribed.

December 18, 1947: The patient had a pharyngitis two weeks ago which subsided on penicillin by mouth. She has had slight ankle edema and there is a little brownish discoloration of the skin of the ankles medially on both sides, suggesting old phlebitis in the deep femoral system of veins. The hemoglobin concentration is 70 per cent (Sahli). The white blood cell count is 7,000 cells per cubic millimeter. The differential count is: 60 per cent polymorphonuclear cells; 37 per cent lymphocytes; 2 per cent monocytes; and 1 per cent basophiles. Her weight is 152 pounds. She has been unable to stay on her diet, but promises to make a greater effort to do so.

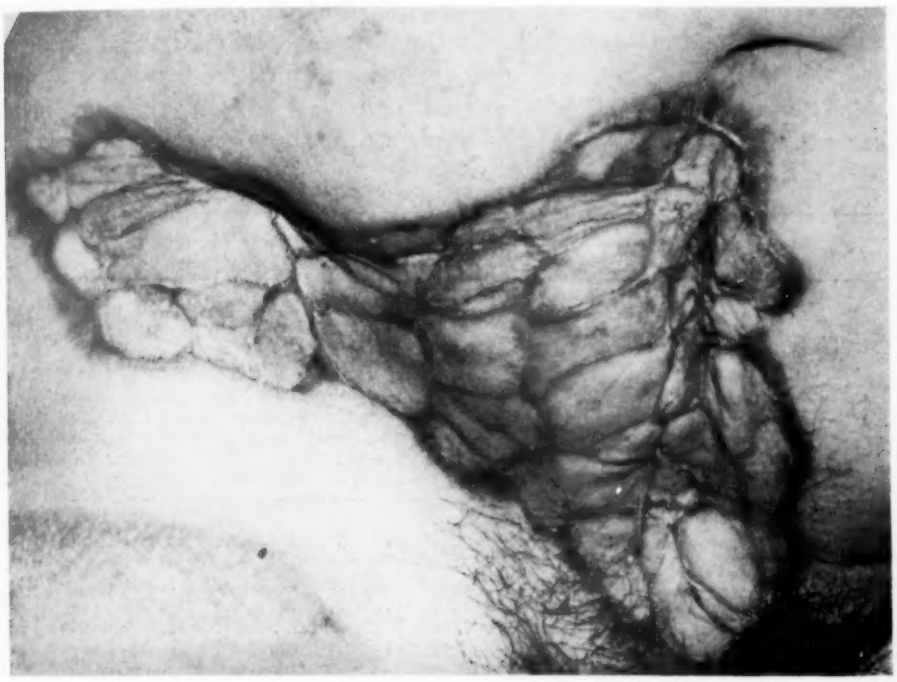

FIG. 5.—Appearance of the grafted area on October 21, 1947, when healing was complete and the grafted skin had become soft and pliable.

DISCUSSION

While it was clear that the principal cause of this patient's illness was the infection of the abdominal wall, the nature of the lesion was obscure. It was a granulomatous infection of the skin and subcutaneous tissue causing ulceration of the skin with blister formation and dissolution of epithelium over abdominal scars and in patchy areas over the infected skin. There was no tendency to form a solitary encapsulated abscess. It had not responded to penicillin and to streptomycin therapy. Because of the leukopenia, a trial of sulfonamide therapy was not made. Activated zinc peroxide had been used at the Jane Brown Memorial Unit of the Rhode Island Hospital on the ulcerated surfaces, but the lesion spread despite it. The opinion of the consulting dermatologist was that the gross appearance of the lesion resembled most closely actinomycosis of the skin or a coccidioides infection.

The lesion was treated as recommended by Meleney[1] for postoperative progressive bacterial synergistic gangrene. The skin of the right lower quadrant of the abdomen was excised beyond the inflammatory margin. Penicillin ointment was used in the dressing instead of activated zinc peroxide. Pathologic examination of the specimen was reported as follows:

"*Abdominal Wall.* The specimen consists of a large irregular segment of skin from the lower abdominal wall, measuring 20 x 16 centimeters with attached subcutaneous fat. There is irregular gray-red ulceration in scattered areas. In other areas there is a peculiar firm nodularity in the surface of cobblestone-like structure. In the outer portion of the specimen is an area in which the epidermis is lifted from the underlying tissue by thin purulent material. On section, several places show a firm fibrous thickening, others a

TABLE IV.—*Additional Laboratory Data from Studies done at Massachusetts General Hospital.*

	Examinations of the Blood												
							Prothrombin Time (seconds)					Cephalin Flocculation	
Date (1947)	*Liver Function (as per cent retention)	Non-Protein Nitrogen (mg. per cent)	Plasma Protein (Gm. per cent)	Albumin Globulin Ratio	Chlorides (milliequivalents per liter)	Vandenberg Reaction	Test Specimen	Normal Control	Cholesterol (mg. per cent)	Phosphorus (mg. per cent)	Alkaline Phosphatase (units per cent)	After 24 Hrs.	After 48 Hrs.
29 May	..	19	6.4	....	95	Normal							
1 June	..	..	....	....	..	.....	18	15	189	...	...	Negative	2+
2 June	22												
21 June	..	..	....	....	..	.....	..	..	...	...	...	Negative	1+
23 June	..	..	....	....	..	.....	..	..	...	4.8	5.2		
24 June	..	24	5.79	1.74	.	Normal	..	..	...	...	...	Negative	1+
25 June	..	..	....	....	..	.....	19	17					
27 June	6												
21 July	..	26	5.92	1.82									
22 July	4												

* Five milligrams of bromsulphalein are injected intravenously per kg. of body weight and the amount remaining in the circulation is determined 45 minutes after injection.

purulent necrosis of the upper layers. *Note:* There is no evidence of fungus infection histologically. *Diagnosis:* 'Acute and chronic inflammation with ulceration and necrosis.'"

The drop in the patient's temperature immediately postoperatively, and the steady improvement in her general condition were remarkable. Nevertheless, in spite of folic acid, ferrous sulphate and crude liver extract, the hemoglobin concentration of the blood by the time she left the hospital was only 11.8 Gm. per cent. An examination of the sternal bone marrow shortly before she was discharged showed no recognizable abnormality. The fluctuating leukopenia, without a frank agranulocytosis, was difficult to explain. It was certainly not related to the administration of penicillin and while penicillin

sensitivity tests against the principal offending organisms showed that the drug was not especially effective against those organisms, the drug was used nevertheless after operation to control secondary invaders in the open lesion during the multiple-stage skin grafting.

It was suspected that the peculiar hematologic response that this patient exhibited to infection and, in addition, the presence of impaired liver function (Table IV), could be due to an intoxication. Her history was carefully searched for possible exposure to noxious agents. The only possibility that could be disclosed was that she might have been exposed to some injurious agents in connection with her work as a hairdresser. Careful questioning revealed no possibility of exposure to carbon tetrachloride or to benzol outside

TABLE V.—*Tabulation of Five Patients Reported by Cotter.*[2]

Case No.	Skin Lesions	Anemia	Leukopenia	Cephalin Flocculation Test	Comment
1	Present. ? X-ray dermatitis.	Hemoglobin 13 Gm. per cent.	None	Positive	Serum phosphatase normal. Recovered 6 months later.
2	Present. Pustules in scalp.	Told she had anemia.	Slight	Strongly positive	Improved thrss months later.
3	Burning and itching of skin strongly positive patch test.	Hemoglobin concentration low.	Granulopenia	Positive	Cephalin flocculation test negative after 3 months.
4	Diffuse itching rash. Patch test positive.	Hemoglobin 10 Gm. per cent. Red blood cell count 3,200,000 per cu. mm.	White blood cell count 3000 per cubic millimeter. Low granulocyte count.	.....	Serum phosphatase 6.1 Bodansky units per cent. Made complete recovery.
5	Slight skin rash. Pustular eruption around roots of hair.	Hemoglobin 10.6 Gm. per cent. Red blood cell count 3.6 million.	White blood cell count 4,600 per cu. mm. Later 4,400 with low granulocyte count.	Positive	Platelets recorded as "scanty" in blood smear. Improved and then had a relapse after her fifth cold wave. No improvement during next 2 months.

of her work. The patient then submitted for examination samples of all the materials and solutions that she has used in her beauty parlor. These were examined by the Division of Occupational Hygiene, Massachusetts Department of Labor and Industries. None of the solutions tested contained benzol or other known toxic agents except for the known presence of thioglycolic acid and/or thioglycolates in cold wave solutions.

The active ingredient in cold wave solutions has already been suspected of exerting toxic effects in man. Cotter[2] has reported cases with leukopenia and liver damage (Table V) which he attributed to intoxication from the active ingredients of cold wave solution. Hardy[3] found leukopenia in two workers engaged in making cold wave solutions. A vacation in both cases resulted in a return of the white blood cell count to normal.

McCord and his associates[4, 5] have made an extensive laboratory study of thioglycolic acid and thioglycolates in different concentrations. They could detect no abnormalities attributable to repeated injections of sodium thioglycolate (3.58 per cent; pH 8.6) into rats and rabbits. With sodium thioglycolate in a cream preparation (7.3 per cent thioglycolate), positive skin patch tests were obtained in 8 per cent of 182 subjects exposed for 24 hours and in seven of 12 subjects exposed for 96 hours. Thioglycolic acid, however, produced positive patch tests even when the exposure of the skin to a 4.6 per cent solution was only for four to six hours.

These workers report that both single and repeated subcutaneous injections of thioglycolic acid produced skin ulcerations which were very slow to heal. Repeated injections, even in small doses, also led to minor changes in the kidney and to more severe changes in the liver. These were interpreted as being reversible. No significant changes were detected in the cytologic examinations of the blood except for a "slight increase in the platelet count." There may have been some lymphocytosis. While pointing out that the condemnation of all cold wave process solutions is not warranted, McCord[5, 6] does state the need for protection of professional beauty shop operators who are exposed to thioglycolates and other cosmetic chemicals. With reference to injections of sodium thioglycolate, it is interesting to note that Brunschwig and his associates[7, 8] found that repeated injections of this compound and certain other sulfhydryl compounds exerted a protective action against the injurious effects of chloroform and carbon tetrachloride upon the liver in dogs and in rats.

It is important to emphasize that it would be hazardous to state categorically that the patient described above owed her peculiar hemocytologic response to infection and the evidence of liver impairment to thioglycolic acid or thioglycolate intoxication. The evidence is purely circumstantial. It is fair to state, however, that as far as intoxications are concerned, this patient had no exposure to any other of the known industrial poisons and none of these could be detected in the solutions with which she worked. The proportion of free thioglycolic acid to its neutralized salt in the solutions with which she has worked cannot be told with any degree of certainty. Nevertheless, from the point of view of occupational medicine, it was thought important to present this case because of the increasing interest in the problem, and because, with accumulation of data from different sources it may be possible to indict or to exonerate cold wave solutions from responsibility in cases such as this "beyond a reasonable doubt."

CONCLUSIONS

1. An unusual case of chronic progressive infectious gangrene of the skin is described.

2. The possible relationship between the manifestations of the infection and exposure to thioglycolic acid and/or thioglycolates in "cold wave" solutions is discussed.

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A STUDY OF THE BETA 17 KETO-STEROIDS IN A CASE OF PSEUDO-HERMAPHRODITISM DUE TO ADRENAL CORTICAL TUMOR*

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EVIDENCE WHICH ATTESTS THE VALUE of determining the beta 17 keto-steroids in the urine when confronted with the necessity of making a diagnosis of the cause of abnormal sexual development is constantly accumulating. The beta 17 keto-steroids as studied in the urine of this one-year-old girl with a masculinizing syndrome conform well to the pattern that has been evolving in this condition. This case is reported for the purpose of adding further confirmatory evidence to the importance of making these determinations.

The keto-steroids have been used as indicators because of the information they convey about the activity of the adrenals. Of all the steroids found in the adrenal gland those which have a keto group on carbon 3, are the ones which possess adrenal cortical function. Thus the interest in so-called keto-steroids. When interest is narrowed down to the adrenal keto-steroids that have action on sexual characteristics, attention is focused on the 17 keto-steroids. The 17 keto-steroids are those with a distinctive side chain on carbon 17. Recently, a further refinement in diagnosis has taken place. The 17 keto-steroids have been divided into alpha and beta fractions and data has been collected upon the relative importance of the beta fraction. When the beta fraction is in pronounced excess, the patient will have an adrenal cortical adenoma or carcinoma. This has been the uniform finding in the reported cases.[4] Thus the surgeon is aided in evaluating the operative indications in a patient with masculinizing changes. If the 17 keto-steroids are high, the pathologic change is probably in the adrenal. If the beta fraction of the 17 keto-steroids is high, the lesion is probably a tumor and not a hyperplasia of the adrenal.

The 11 oxy-cortico steroids with a 17 hydroxyl group were also studied. Talbot and his associates,[1] state that these substances result from adrenal cortical activity and are an index of the rate of secretion of adrenal cortical hormones influencing protein and carbohydrate metabolism. They have found these substances excreted in abnormally large amounts in patients suffering from burns and postoperative conditions as well as in Cushing's syndrome and adrenal cortical virilism. No abnormal elevation was found in simple hirsutism.

CASE REPORT

A one-year-old white female was referred for admission to the Buffalo Children's Hospital on November 17, 1946, by Dr. Max Landsberger. The mother stated that she had first noted a single black pubic hair when the child was 3 months old. At the age of

* Submitted for publication, June 1948.

11 months, the Pediatrician first noted an enlarged clitoris and numerous pubic hairs during a routine physical examination. His examination a month previously had not disclosed this abnormality. The child had no complaints and behaved normally.

Examination revealed a healthy appearing young female weighing 25 pounds. Development appeared normal with the exception of the prominent pubic hair and axillary hair. The clitoris was enlarged to four times normal size, also the labia majora. No abdominal masses were found nor were any palpated by rectum. The blood pressure was 100 systolic and 70 diastolic.

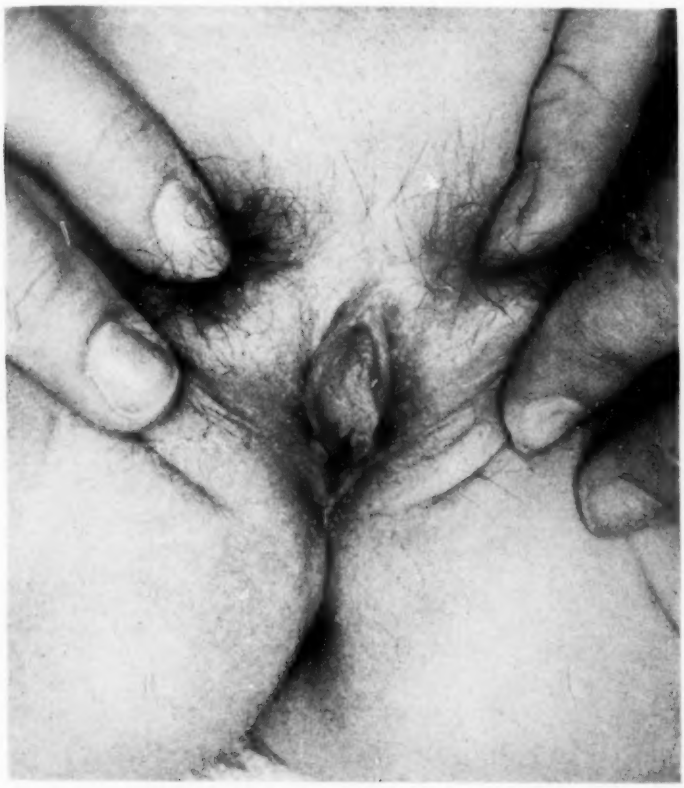

FIG. 1.—Preoperative appearance of clitoris showing growth of pubic hair.

Roentgen-ray studies of the sella turcica and the bones of the skull revealed no abnormalities. The bone age of the long bones were consistent with the child's age. A plain film of the abdomen showed a deformity in the gas-filled duodenum. The duodenum had a concavity in its right border and was displaced to the left as far as the midline. This finding, suggestive of a mass in the region of the right kidney, deforming the duodenum was confirmed after filling the duodenum with barium. It was also illustrated by intravenous pyelography which showed the pelvis of the right kidney to be displaced downward.

Examination of the blood and urine was within normal limits. The serum chlorides were 105 M.Eq., non protein nitrogen 22 mg. per cent, sodium 138 M.Eq., cholesterol 175 to 213 mg. per cent, blood sugar 71–123 mg. per cent.

The total 17 keto-steroids were 88.8 mg. in a 24 hour urine sample. The beta fraction of these amounted to 79 mg. The 11 oxy-cortico steroids were 1.07 mg. in 24 hours.

The child's abdomen was explored through an upper transverse incision. A large retroperitoneal tumor mass the size of a man's fist was found at the upper pole of the right kidney. This was excised in toto. The postoperative course was entirely uneventful.

The microscopic description of the tumor by Dr. Kornel Terplan stated that it showed a uniform picture of a mature tubular and alveolar adrenal cortical adenoma of the typical pattern described as the basis of the adreno-genital syndrome. The tumor was well encapsulated and showed some calcification in the hyaline capsule. The tumor cells were rich in glycogen and lipoid. There were but few atypical giant nuclei. Two weeks

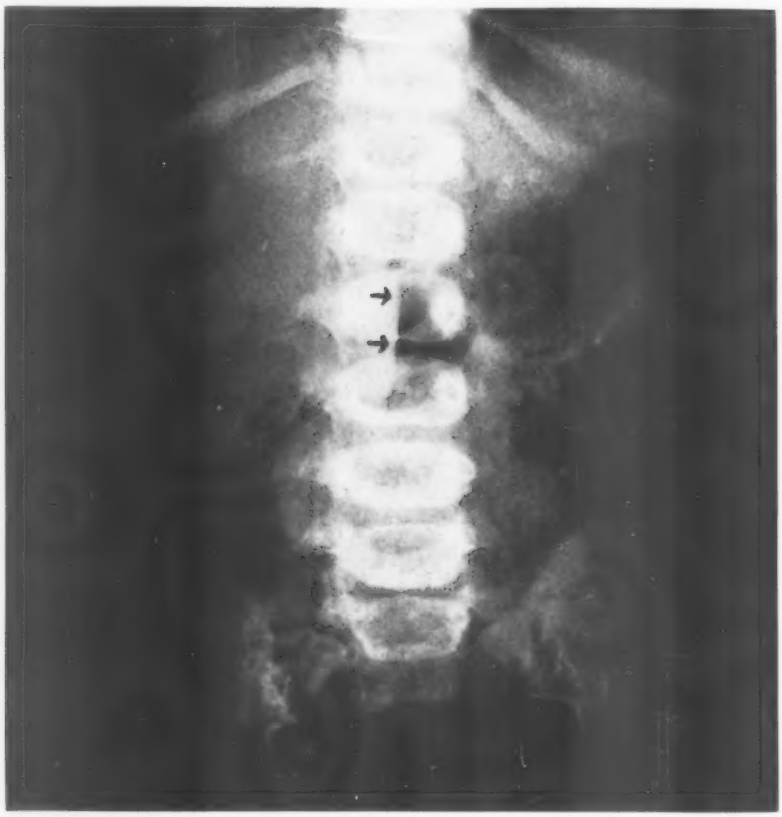

FIG. 2.—Plain roentgenogram of the abdomen. Arrows show air-filled duodenum deformed by the tumor.

after operation none of the 17 keto-steroids was found in the urine. The 11 oxy-cortico steroids had fallen to .04 mg. in a 24-hour urine sample. A year after operation the total 17 keto-steroid excretion in 24 hours was .2 mg. fraction and the 11 oxy-cortico steroids were .04 mg. (Fractionation of the total 17 keto-steroids was not done because the total value was too low.) At this time the clitoris had diminished in size and the pubic hair was less dense and of finer texture. The child was otherwise normal.

COMMENT

Gross[2] in 1940 described numerous neoplasms which produced endocrine disturbances in childhood. These vary greatly. There may be slow growing

tumors of neurogenic origin of the floor of the third ventricle which produce precocious appearance of the secondary sex characteristics. The secondary sex characteristics, however, are always the same as would be expected according to the child's sex. Likewise, a precocious puberty due to a neoplasm is found where the tumor is in the pineal gland. This is always seen in boys. Granulosa cell tumors of the ovary with their masculinizing changes were found producing precocious puberty in girls. No arrhenoblastomas of the ovary with their masculinizing changes were found as they do not occur in children. The youngest recorded patient with arrhenoblastoma was 15. In this review, carcinoma of the adrenal cortex was described as producing

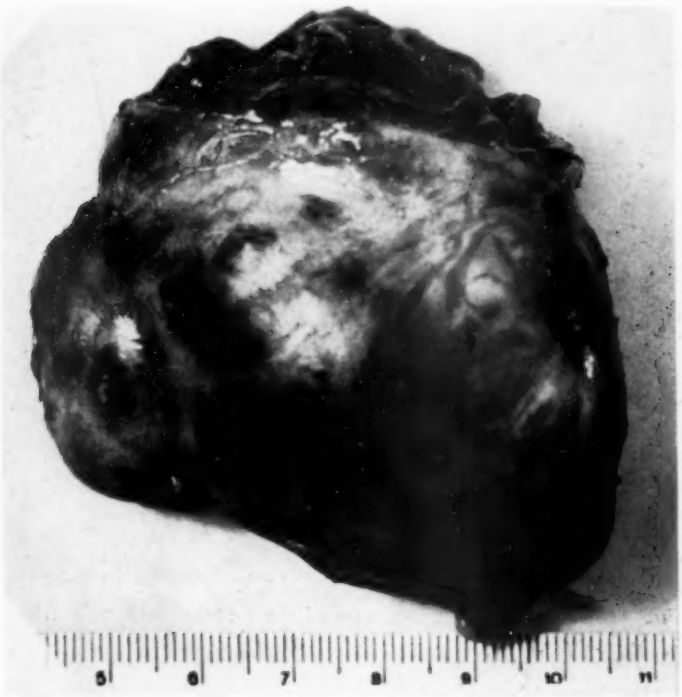

FIG. 3 A.—Gross appearance of the resected adrenal cortical adenoma.

Cushing's syndrome, a masculinizing syndrome in females and a feminizing syndrome in males. A testicular tumor composed of interstitial cells was found to produce early changes in the secondary sex characteristics in a male child.

Talbot, Butler and MacLachlan[3] in 1940 found the 3 beta hydroxy-17-keto-steroids to amount to 10 per cent of the total 17 keto-steroids in normal persons. In two girls with adrenal tumors the proportion was 50 per cent and 63 per cent.

Talbot, Butler and Berman[4] in 1942 stated that patients with adrenal cortical hyperplasia and those with adrenal carcinoma both excrete abnormally large amounts of the 17 keto-steroids. The minimum values of the carcinoma patients approximately coincide with the maximum of the hyperplasia group. Only the group with carcinoma excrete definitely increased quantities of beta 17 keto-steroids.

Callow and Crooke[5] in 1944 summarized the data on 19 reported cases of adrenal cortical tumors. In all but two of these 19 cases the daily output of 17 keto-steroids exceeded four times the average normal excretion. They emphasize that patients with pre-pubertal virilism without adrenal tumors may show relatively the same values (34 to 64 mg. per 24 hours) for urinary

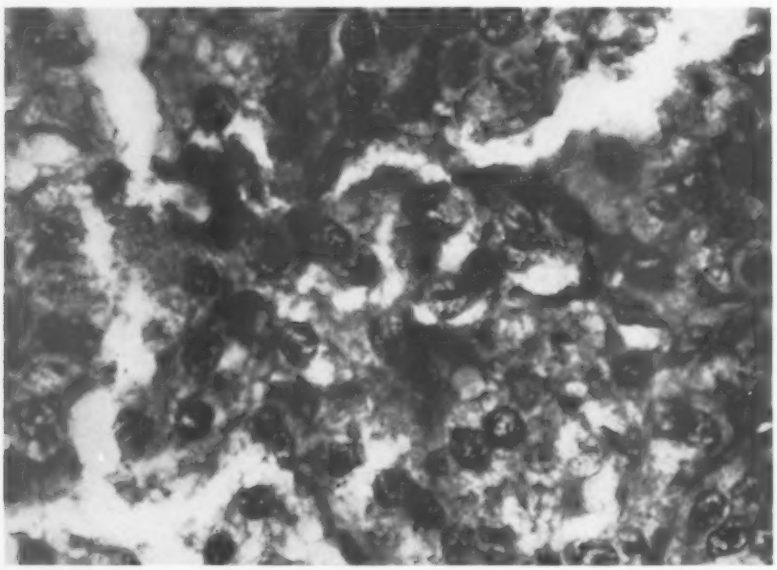

FIG. 3 B.—Microscopic appearance of the resected adrenal cortical adenoma.

17 keto-steroids as the lower range of 17 keto-steroid output in similar patients with adrenal tumors. They report a case of a girl, age 14, whose menstrual periods began at the age of 10. At the age of 12, she developed a large clitoris and hair grew on her face. The total 17 keto-steroids were 90 mg. The beta fraction only accounted for 12 per cent of this total. At operation, normal adrenals and ovaries were found.

Cantarow and Trumper[6] in 1945 stated that the total 17 keto-steroids showed high values in adrenal cortical carcinoma, adrenal cortical hyperplasia and interstitial cell tumors of the testis. They found the beta fraction high in adrenal cortical carcinoma exhibiting the adreno-genital syndrome, also in adrenal cortical carcinoma producing Cushing's syndrome and in one male patient with feminization resulting from adrenal cortical carcinoma.

Broster and Gardener-Hill[7] in 1946 produced a marked improvement in a case of Addison's disease by transplanting an adrenal gland from a case of virilism in a young woman. The donor girl, whose 17 keto-steroids were 29.5 mg. prior to operation, provided an hypertrophied left adrenal gland. Following operation her 17 keto-steroids fell to 5 mg. and she made a satisfactory psychosomatic adjustment. The recipient, who could not be maintained in health without salt and cortical hormone substitution therapy, was able to lead a normal life after having this adrenal gland embedded in her left rectus muscle and anastomosed to the deep epigastric artery.

Dockerty[8] in 1947 described the arrhenoblastoma as the most common functioning ovarian tumor that produces masculinizing changes. While it produces androgenic substances, they are not excreted as 17 keto-steroids. Thus there is a method of differentiating the ovarian masculinizing syndrome from the adrenal masculinizing syndrome. Of much more rare occurrence is the masculinovoblastoma (adrenal-like ovarian tumor). To masculinization, this tumor adds other features of Cushing's syndrome such as hypertension, plethoric obesity, diabetes and polycythemia. The results of hormonal studies in this tumor have been somewhat at variance.

Johnson and Nesbit[9] in 1947 have presented an excellent survey of the literature and details of the 17 keto-steroid excretions in adrenal cortical carcinoma. They found only 32 cases of adrenal cortical carcinoma in which the total 17 keto-steroids had been done and a very few where the beta fraction had been determined. They added three cases of their own in which not only did they find a marked elevation of the total 17 keto-steroids but also the expected increase in the beta fraction which comprised respectively 57, 74 and 80 per cent of the total.

We are deeply indebted to Dr. Fuller Albright of Boston, Massachusetts, in whose laboratory the determination of the keto-steroids were made.

CONCLUSIONS

1. This case of pseudo-hermaphroditism with a surgically removed adrenal cortical adenoma has shown the expected elevation of the total 17 keto-steroids (88.8 mg.) and the percentage (87 per cent) of 3 beta hydroxy-17 keto-steroids.

2. The 11 oxy-cortico steroids were found to be four times the average normal in this case. This is likewise consonant with reported studies on adrenal cortical tumors.

3. Follow up studies a year later showed a return of the keto-steroids and oxy-cortico steroids to normal and some regression in the masculinizing changes.

This is presumptive evidence that there has been no recurrence of the tumor.

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EVALUATION OF THE OPEN JUMP FLAP FOR LOWER EXTREMITY SOFT TISSUE REPAIR*†

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A RAPID EFFICIENT METHOD of transferring large flaps of skin and subcutaneous tissue to resurface scar defects of the lower extremity has been developed by Cannon, Brown, Lischer, *et al.*, during the recent war. The commonly used abdominal tube pedicles have taken many months to complete and some have been lost in transit. The open jump flap from the abdomen, however, has been found to be much safer, and transfer of large flaps can be completed in a much shorter time.

As the above authors have pointed out, the fundamental principles of the open jump is maintenance of a short broad pedicle throughout all stages of transfer. This assures the flap of an adequate blood supply at all times and allows the use of very large areas of abdominal skin and subcutaneous tissue. A wider area of scar on the leg can be covered with the open jump flap since the abdominal tube is necessarily restricted in its width. The open jump flap method has been used to cover defects from the inguinal region to the sole of the foot, and to the level of a stiff knee. The contralateral arm is often used for a carrier in covering defects of the foot. The open jump flap has the advantage over the cross thigh or cross leg flap in that there is no danger of impairment of circulation in the opposite leg.

TECHNIC. The most important step in preparing an abdominal flap is careful planning. Either arm may be used as a carrier, and the flap may be attached to the radial or ulnar side of the forearm, depending upon which, in the individual case, will allow the most comfortable position during transfer. The flap should always be made one-third larger than the defect to be covered to allow for shrinkage.

A rectangular abdominal flap is raised and dissected back along the deep fascia to preserve the blood vessels running just above the fascia. This flap is so placed on the abdomen that the forearm can be comfortably attached with a minimum of tension. Another rectangular flap of the same width is raised on the forearm. This flap should be one to one and a half inches in length so that when it is turned back an open area of two to three inches in length and the same width as the abdominal flap will be present for attachment

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† This work has been done in association with Colonel James B. Brown, Lieutenant Colonels Bradford Cannon, David Fisher, and Majors Carl E. Lischer, William B. Davis, Stephen Chasko, Andrew M. Moore, Joseph E. Murray, Pierson Checket, and Stephen R. Lewis, and Captains Milton Edgerton, James E. Jensen, Allyn McDowell and Franklin T. Buchannan.

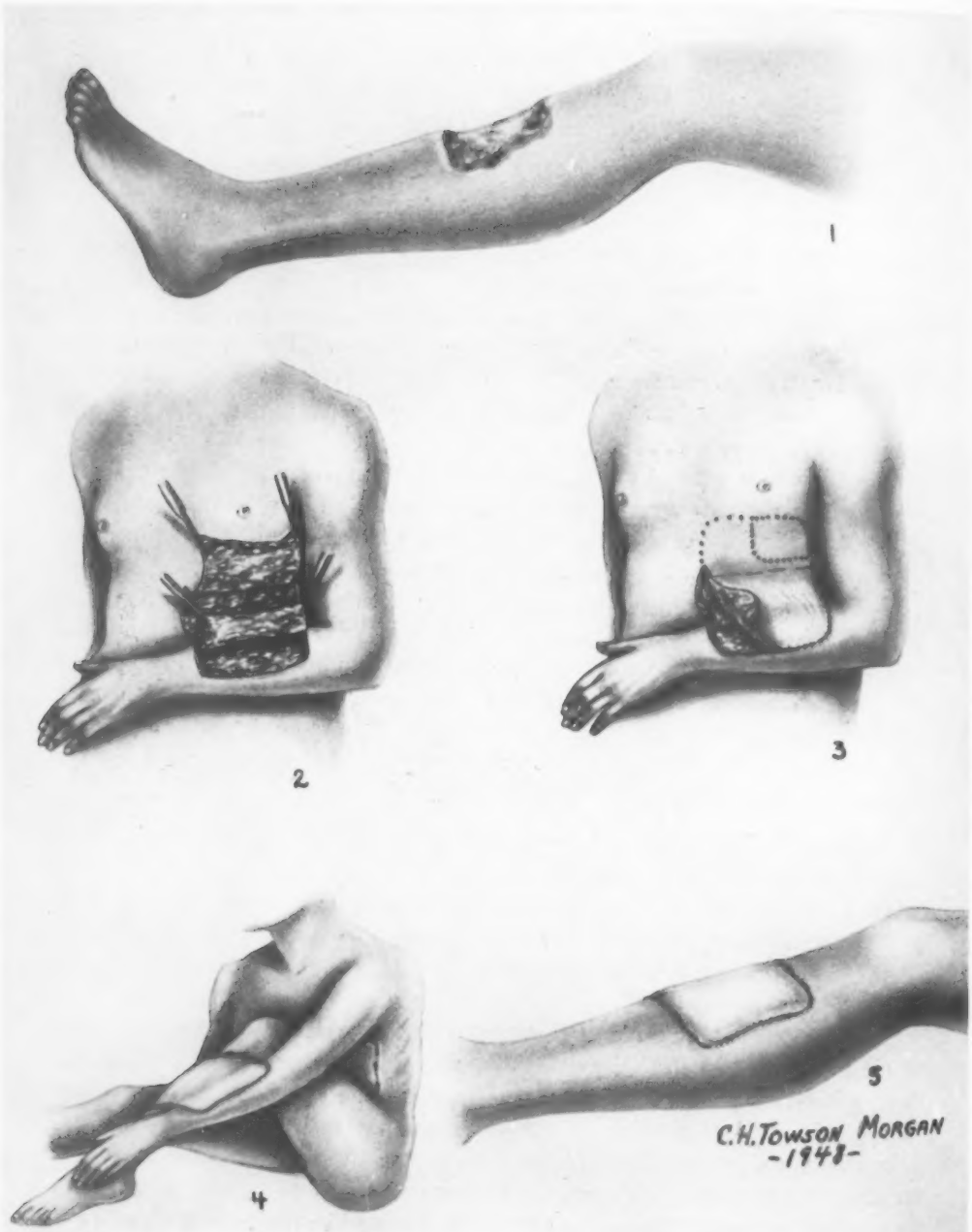


FIG. 1.—1. The defect to be covered.

2. The abdominal and arm flaps raised and ready for attachment.

3. The open jump flap partially sutured to the arm flap. Outer dotted lines indicate remainder of the proposed flap on the abdomen. Inner dotted lines on the left outline area to be undermined at the first delay.

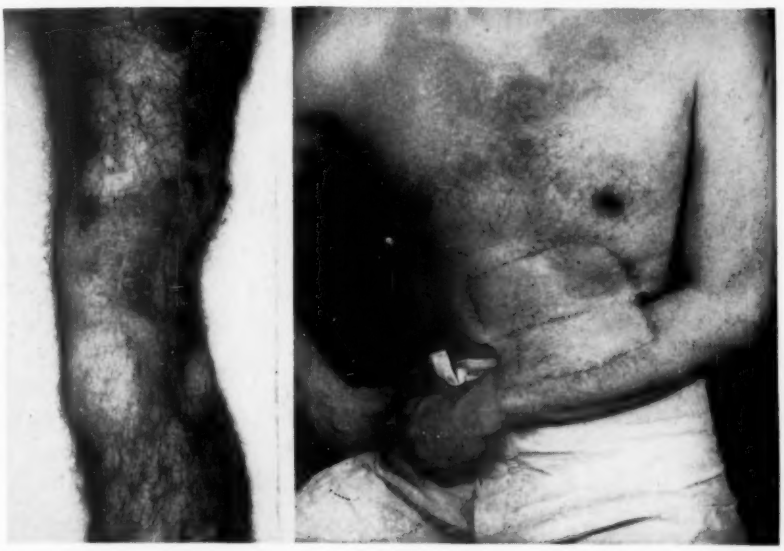
4. The open jump flap attached to the leg.

5. Completed open jump flap.

of the abdominal flap. The two flaps are then sutured together and the open area on the abdomen covered with a skin graft.

After two or three weeks, one-half of the proposed flap remaining on the abdomen is outlined, completely undermined, and resutured in its original position. Ten days later this procedure is repeated on the other half of the proposed flap. The purpose of these delays is to improve the collateral circulation nourishing the flap from the forearm.

Seven to 14 days later the entire flap is raised from the abdomen, and the abdominal defect covered with a split graft. The operating table is now jackknifed and the patient brought to a sitting position so that the arm and leg may



A B

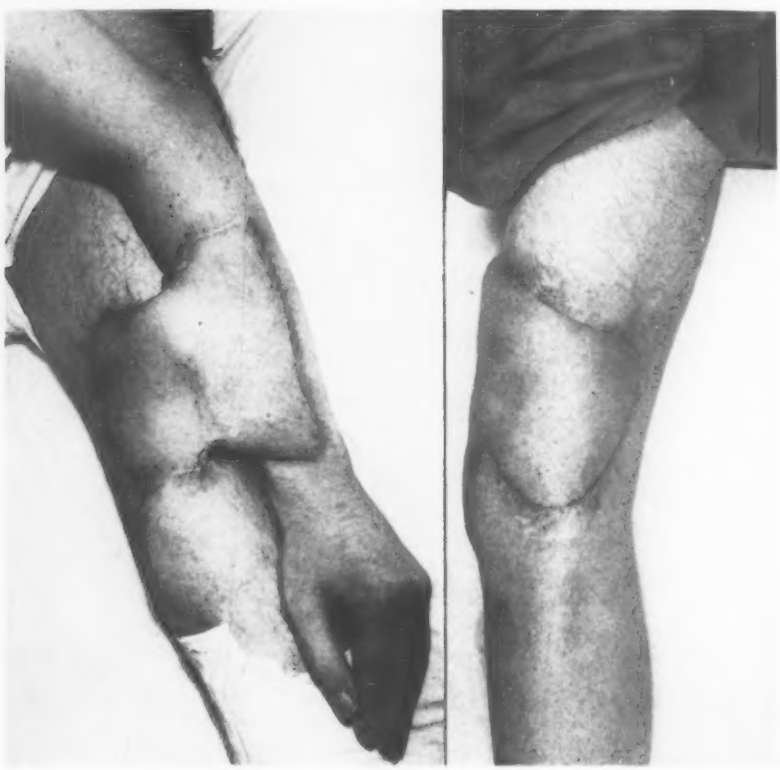
FIG. 2.—A and B. Stages in construction of an open jump flap for resurfacing scar tissue of the left thigh in a patient who needed a bone graft to the left femur.

be approximated. Skin and scar tissue are excised from the leg defect and the jump flap carefully sutured in place. A pressure dressing is applied and the arm is taped to the leg. The patient's body is held in a flexed position at the hips by a body and leg cast or by long strips of adhesive, as the case requires. This procedure is usually carried out under low spinal anesthesia supplemented on the abdomen by novocaine infiltration for detaching the flap and applying skin graft. This allows the patient to cooperate and avoids the dangers of a thrashing patient awakening from a general anesthesia.

In three weeks the flap is two-thirds detached from the arm, and resutured. Three to seven days later the flap is completely detached and inserted into the leg defect after removing the remaining scar. The flap on the arm may be resutured at this time and usually leaves little more than a linear scar.

EVALUATION

An attempt has been made to compare the efficiency, period of time required for completion and safety of the abdominal tube pedicle with that of the open jump flap for covering defects of the lower extremity. The abdominal tube pedicle method of resurfacing leg defects was selected for comparison because it was the most common method used by the Plastic Surgical Service at Valley Forge General Hospital and many other plastic surgical services for covering defects too large to be adequately covered by cross leg flaps or by local



C D

FIG. 2.—C and D. Stages in construction of an open jump flap for resurfacing scar tissue of the left thigh in a patient who needed a bone graft to the left femur.

flaps. To do this, 26 open jump flaps and 33 abdominal tube pedicles used for lower extremity repair at Valley Forge General Hospital during 1946 and 1947 have been carefully studied and compared. The same surgeons worked on both types of tissue transfer, and the majority of the surgeons performing these procedures has had approximately the same amount of surgical experience.

Of the 33 abdominal tube pedicles studied, seven were unsuccessful to the extent that another abdominal tube or some other method of coverage was

necessary for resurfacing the defect. These tube pedicles were lost at various stages of transfer, usually because of thrombosis in the tube, or necrosis at the distal end. Twenty-six abdominal tube pedicles were successfully completed. It was found that the average length of time that elapsed from the first operation for construction of these 26 abdominal tubes to the date of insertion of the tube into the scar tissue defect was 333 days or approximately 11 months. An average of ten operations was necessary in the 26 completed tubes.

Twenty-six open jump flaps were completed during 1946 and 1947. A corner of one flap was lost, necessitating a small local flap; all other flaps were completely successful. An average of 104 days, or approximately three and one-half months, elapsed between the original operation of attachment of the jump flap to the forearm, and insertion of the flap into the defect. An average of six operations were required in these 26 cases.

The primary objection that has been raised to the open jump flap is the fact that the open under-surface of the flap violates the closed wound principle of surgery. This objection can easily be overcome by covering the under-surface of the flap with a thick split graft. Several of the flaps in the above series were constructed, maintaining a closed wound through all stages; yet these flaps seemed to have no advantages over those left open.

SUMMARY

The open jump flap method of repair of soft tissue defects of the lower extremity is described.

Twenty-six open jump flaps and 33 abdominal tube pedicles were reviewed.

Open jump flaps were completed in an average of 104 days and six operations as compared to an average of 333 days and ten operations for completion of the abdominal tube pedicles. Thus, the open jump flaps took only one-third the time required for abdominal tube pedicles.

One open jump flap was partially lost as compared with seven unsuccessful abdominal tube pedicles.

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CARCINOMA DEVELOPING IN SEBACEOUS CYSTS*

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WE HAVE RECENTLY REVIEWED THE CASES OF CARCINOMA developing in sebaceous cysts from the material of the Department of Surgical Pathology at the Barnes Hospital. The relatively large amount of material available as well as certain other desirable data appeared to justify a report of our analysis. It has been the practice at this hospital to examine histologically all excised tissue whether apparently benign or not. Sebaceous cysts removed on both the ward service and the private service are routinely submitted for microscopic study, so it is thought that the incidence of malignant transformation may be stated with some accuracy in this report. In three relatively large series reported previously on this subject only Bishop[1] examined microscopically all cysts removed, both Caylor[2] and Stone and Abbey[3] studying microscopically only those cysts in which there was some reason for suspecting a carcinomatous change.

That cutaneous epithelial cysts have several possible origins is well recognized and yet "sebaceous cyst" has come to be applied rather loosely to most cysts of the skin without regard for their origin. This is not without some justification as differentiation may be extremely difficult or impossible particularly when inflammation and degeneration occur. Sebaceous cyst becomes a most infrequent lesion when rigidly defined, as by Warvi and Gates,[4] as retention cysts of sebaceous glands in which secreting sebaceous gland cells must form an integral part of the lining wall. They found only three out of 566 cutaneous epithelial cysts which satisfied these criteria and felt that many more epithelial cysts arise from congenital inclusions or from epithelial cells misplaced by injury. Franke[5] has reported a malignant transformation in what probably was a true traumatic epithelial cyst of the base of the thumb, and one of Collins'[6] three cases may represent carcinoma originating in a traumatic epithelial cyst on the palmar aspect of the finger. In none of our cases was there any reason to suspect such a course. Broders and Wilson[7] feel that most so-called sebaceous cysts are better classified as keratomas, and they note several points of differentiation. However, in past reports of carcinoma developing in epithelial cysts, there have been only infrequent efforts made to define the origin of the cyst, and it has been customary to refer to them as "sebaceous cysts." Love and Montgomery[8] reported two carcinomas developing in epithelial cysts other than sebaceous

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cysts and two carcinomas developing in sebaceous cysts, and yet they note that a sharp distinction between the various types of benign cyst has not always been made in their 271 cases. In our material it has not been customary to break down the cysts of the skin of this type into finer subdivisions, and in those cases where carcinoma appears, this differentiation is difficult if not impossible.

It is not always possible to determine from histologic examination alone whether a particular skin cancer has its origin in a cyst. We have in all cases reviewed the history in association with the gross and microscopic

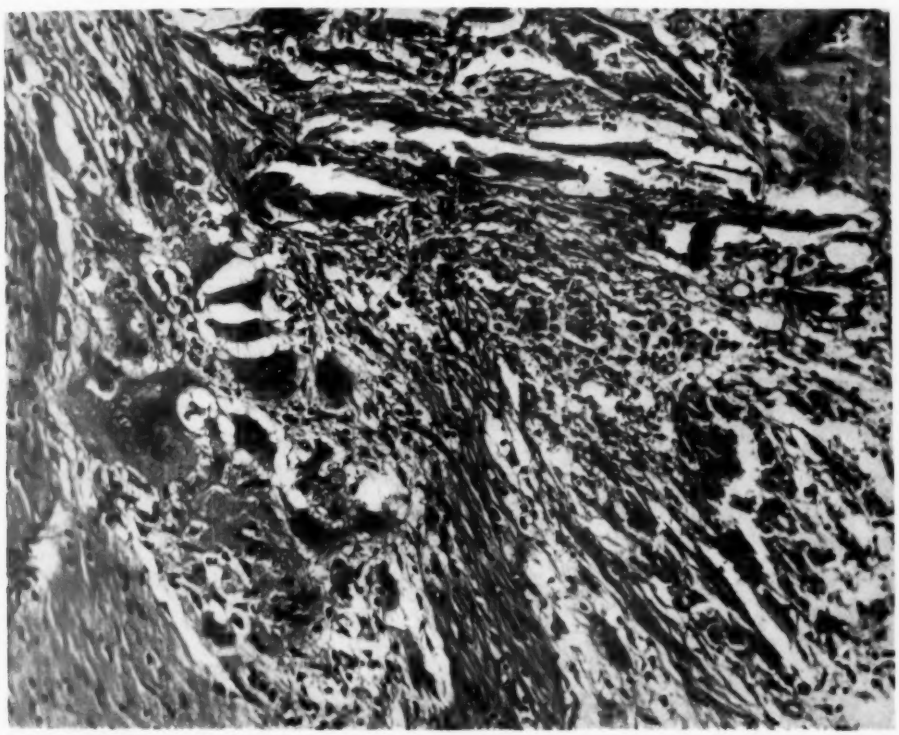


FIG. 1.—Foreign body inflammatory reaction adjacent to sebaceous cyst in which cancer developed. (230x)

findings and in some instances have relied chiefly on the history in determining the origin of a particular lesion. In some cases inflammatory changes in response to the irritable contents of a sebaceous cyst may be seen and give a clue to the cyst origin of the carcinoma (Fig. 1). Even with all available information there may still be some doubt, in which case we may have been inclined to favor the side of cyst origin. In our 14 cases the histologic evidence in nine has been conclusive of the sebaceous cyst origin of the carcinoma; in the five remaining cases we have relied on other evidence in addition to the histologic appearance usually suggestive of cyst origin.

INCIDENCE

Carcinoma developing in sebaceous cysts has been frequently reported in the literature although usually in small numbers in individual series. However, Ricker and Schwalbe[9] in 1914 collected 43 cases from the literature and there have been a number of cases reported since then.[1-3, 6, 8, 10-15] Bishop[1] reported 11 cases and in his material the incidence of malignant change in a sebaceous cyst was 9.2 per cent, the highest figure in the literature. In other relatively large series Caylor[2] has found the incidence of this change to be 3.4 per cent, Stone and Abbey[3] 2.2 per cent and Love and Montgomery[8] 1.5 per cent. We have identified 14 carcinomas having origin in sebaceous cysts while examining 818 benign sebaceous cysts, an incidence of 1.7 per cent. At the same time 536 squamous cell carcinomas of the skin have been studied, so that our cases make up 2.6 per cent of this group. On the basis of this information, we agree with Love and Montgomery[8] that sebaceous cyst need not be considered as a precancerous lesion. The frequency of malignant change in the group of dermatoses classified as precancerous by Montgomery,[16] namely Bowen's disease, senile keratosis, keratoses resulting from arsenic, tar or radiation and leukoplakia of the mucous membranes, is 20 per cent or more. On the other hand, Sutton[17] and Hellwig[18] criticize the use of the term precancerous at any time.

AGE, SEX, RACE

The average age of our patients was 51.6 years in accord with previous series[1-3, 6, 9] and only one patient was under 40 years of age. Bishop[1] has noted an average age of 38.2 years of patients with benign sebaceous cysts removed, so the possibility of carcinomatous change appears to be greater with increasing age. The sex distribution was equally divided; there were six males and eight females in our group. One carcinoma occurred in a colored female.

SITE, DURATION

Seven cases occurred on the scalp, two on the face and one each on the ear, shoulder, arm, forearm, and thigh. In other reports[1-3, 6, 9] the lesions have occurred predominantly above the shoulders with the face and the scalp the most common sites. Approximately one-fourth of all benign sebaceous cysts removed occur on the scalp.[2] No basal cell carcinomas of the scalp originating in sebaceous cysts have been reported in the literature.

Only three of our cases are of known duration greater than two years, one 25 years and two 15 years, while only three cases are of known duration less than 18 months. The relatively long duration of these lesions is apparent.

TRAUMA, ULCERATION, PREVIOUS EXCISION

The influence of trauma or irritation in the malignant change of sebaceous cysts has been variably considered of importance[8, 13] and of no significance.[1-3] In spite of the frequent appearance of these lesions on the scalp, only one

TABLE I.

Cases	Age	Sex		Site	Duration	Irritation; Trauma	Ulceration	Previous Excision	Recent Change in Character	Preoperative Diagnosis	Histologic Dx	Metastases	Follow-up
1. M.T.	43	F	W	Scalp	15 yrs.	0	0	0	Gradual increase in size 1 yr.	Seb. cyst	Squamous cell ca.	0	Well, 7 yrs.
2. R.G.	66	M	W	Cheek	6 wks.	Pin prick 1 yr. prev.	0	0	0	Epithelioma	Squamous cell ca.	0	Well, 2½ yrs.
3. J.M.	44	M	W	Arm	1½ yrs.	Squeezed	0	0	Recent pain	Seb. cyst	Ca. unclassified	Yes	Well, 11½ yrs.
4. F.N.	63	F	C	Scalp	15 yrs.	Traumatized with comb	Yes	Yes; 5 yrs. prev.	0	Sarcoma	Squamous cell ca.	0	Well, 7 yrs.
5. J.J.	43	M	W	Face	8 wks.	0	0	"Lanced" 5 wks. prev.	Recent increase in size	Tumor	Squamous cell ca.	0	Well, 6 yrs.
6. M.R.	64	F	W	Forearm	3–4 wks.	0	0	0	Rapid growth	? Tumor	Squamous cell ca.	0	Died 5 yrs. later of "stroke" with no evidence of recurrence
7. H.C.	25	M	W	Thigh	?	0	0	0	0	Seb. cyst	Squamous cell ca.	0	No follow-up
8. I.M.	48	F	W	Scalp	25 yrs.	0	0	0	Recent increase in size	Seb. cyst	Squamous cell ca.	0	Recurrence—2 yrs. Re-excision elsewhere, well 4 yrs.
9. C.W.	63	F	W	Shoulder	2 yrs.	0	0	Yes; 3 wks. prev.	Recent pain	Infected seb. cyst	Squamous cell ca.	0	Well, 10 yrs.
10. A.K.	75	F	W	Scalp	2 yrs.	0	0	0	0	Seb. cyst	Squamous cell ca.	0	Well, 5 yrs.
11. B.W.	53	F	W	Scalp	?	0	0	0	0	? Tumor	Squamous cell ca.	0	Well, 3 yrs.
12. A.V.	57	M	W	Scalp	Years	0	0	0	Recent increase in size	Calcified seb. cyst	Squamous cell ca.	0	Well, 3 months
13. T.T.	79	M	W	Ear	1½ yrs.	0	0	Yes, 6 wks. prev.	0	Basal or squamous cell ca.	Squamous cell ca.	Yes	Unresectable metastases
14. R.C.	X	F	X	Scalp				No history		Seb. cyst	Squamous cell ca.	0	No follow-up

of our cases reported irritation of the lesion on combing the hair, and only two others of the entire group reported trauma of any other sort. Probably more of these cysts were subject to the trauma of squeezing than is reported, and yet one can find little justification for assuming that trauma is of significance in the carcinomatous change. Only one of our cases gave a history of discharge or ulceration although ulceration in a sebaceous cyst should probably be regarded with suspicion.[2, 3, 8] Three cases had a previous excision within six weeks of treatment at our hospital and one five years previously. This does not appear to be a significant factor in the appearance of cancer in these cases.

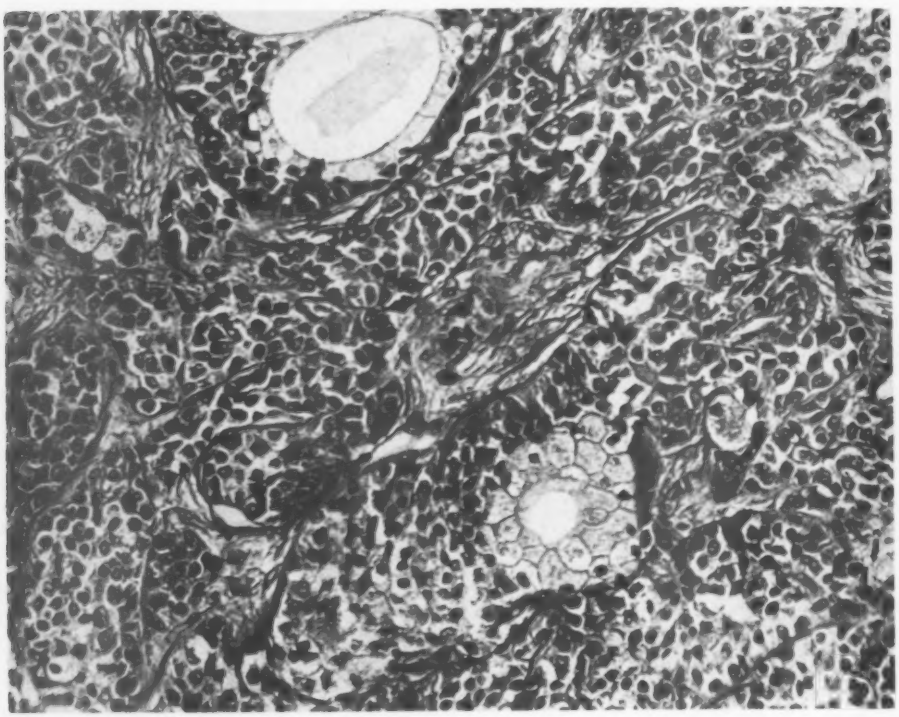


FIG. 2.—Case 1. Compact masses of large clear cells showing gland formation in some areas. (230x)

CHANGE IN CHARACTER

In five cases there was observed by the patient a recent change in the character of the lesion. In two instances pain developed and in three cases a recent increase in size of the lesion was noted. Although other reports have not stressed this factor, certainly an increase in size of the lesion should arouse suspicion, particularly if it occurs without evidence of irritation or inflammatory changes.

PREOPERATIVE DIAGNOSIS

As one might suspect, the preoperative diagnosis was incorrect in the majority of cases, and the most common diagnosis was benign sebaceous cyst. In only one instance was the correct diagnosis of squamous cell carcinoma made although the clinician did not definitely associate the lesion with a pre-existing sebaceous cyst. In four other cases tumor of some sort was diagnosed. While this is hardly an enviable record, the errors in diagnosis have not appeared to be of great significance in the final result in these cases.

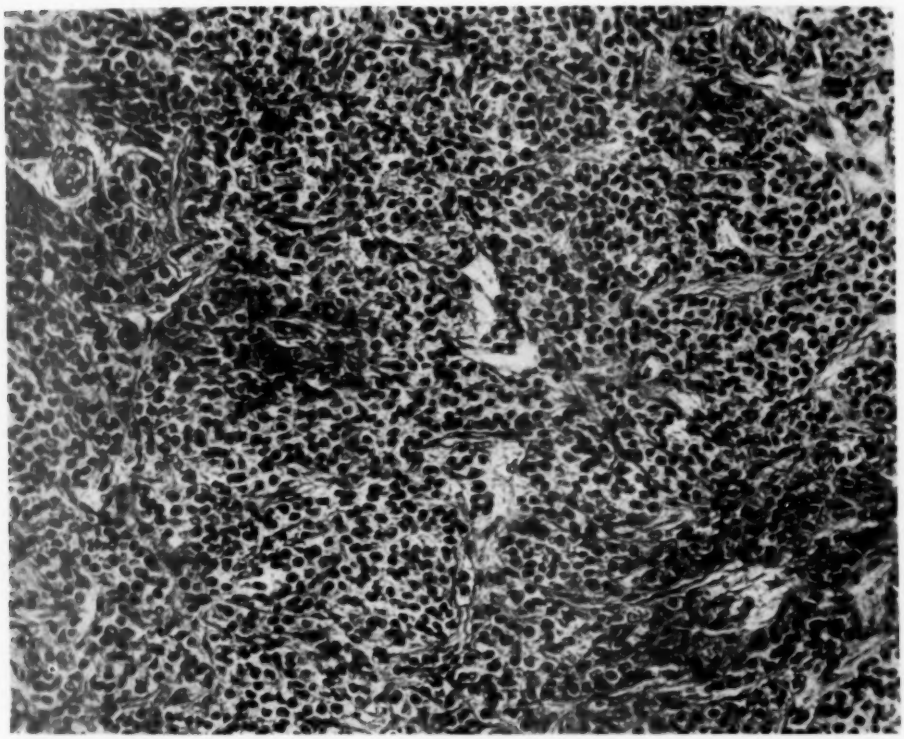


FIG. 3.—Case 1. Metastasis to axillary lymph node showing cells similar in appearance to those of the primary tumor. (170X)

PATHOLOGY

Carcinoma developing in a sebaceous cyst is predominantly of a squamous cell type, although basal cell growth may be found in approximately 15 per cent of cases.[6] However, no basal cell carcinoma of such origin has been reported on the scalp although 35 per cent of malignant sebaceous cysts have been found in this area. Most of the squamous cell carcinomas are well differentiated and of low grade malignancy with marked keratinization and pearl formation (Fig. 5). Havens[19] briefly records a case in which a

melano-epithelioma appeared in a keratoma of the scalp, but this is the only recorded instance in the literature of a growth other than squamous cell or basal cell carcinoma developing in a sebaceous cyst. We have found no specific mention of a carcinoma originating in a sebaceous cyst in which the cells have retained the characteristics of the cells of the sebaceous gland. Of our cases 13 were squamous cell carcinomas showing good differentiation and there were no basal cell growths. One case we have not classified because of its atypical appearance. This case is briefly reported here.

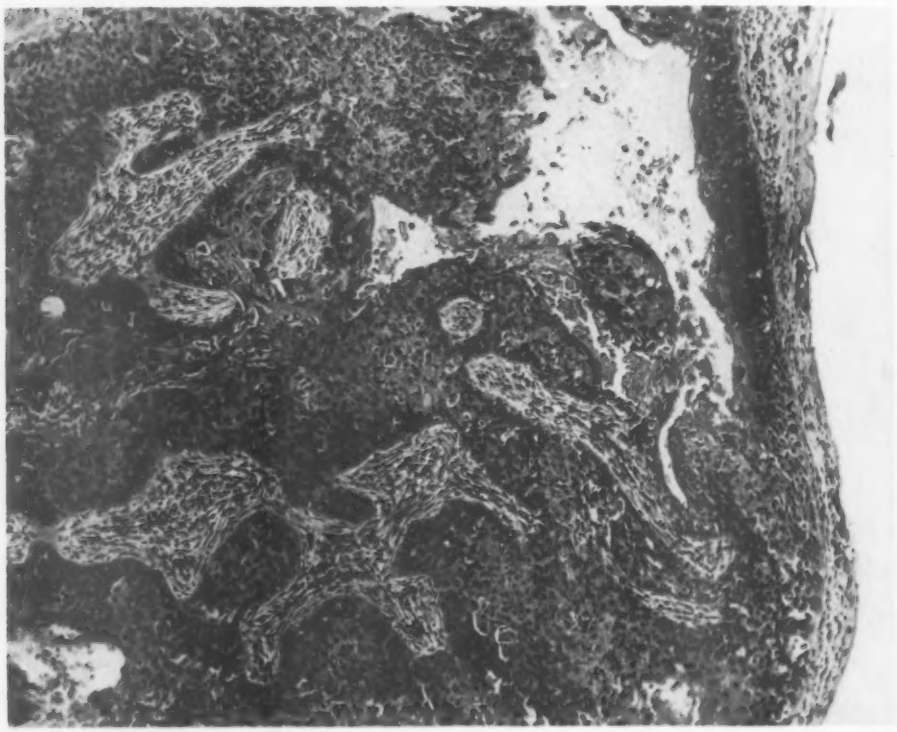


FIG. 4.—Carcinoma in wall of sebaceous cyst with growth into lumen. (85x)

Case Report No. 1.—A 44-year-old white male first noted a small pimple on the lateral side of the left arm at its mid-portion 18 months before first seen at Barnes Hospital. This lesion produced a small amount of blood when squeezed. There was a gradual increase in size and finally some pain. On examination the lesion was the size of a hickory nut, movable, attached to the skin and not ulcerated. There were no palpable lymph nodes. The preoperative diagnosis was sebaceous cyst, but on removal a carcinoma was found, apparently originating in a sebaceous cyst and made up of cells with a vacuolated cytoplasm and large vesicular nuclei reminiscent of sebaceous gland cells. The cells were arranged in cords and compact masses with some attempt at gland formation; other areas showed a tendency to squamous cell carcinoma (Fig. 2).

Ten months later several small but palpable, enlarged nodes were found in the left axilla and one enlarged node in the right axilla. There was an apparent increase in size

of the left axillary nodes over a two week observation period, so a radical dissection of the left axilla and a biopsy of the right axillary node was done. Microscopic examination showed the right axillary node to be free of disease but one node from the left axilla was almost entirely replaced by carcinoma made up of compact masses of cells similar in appearance to those of the primary tumor (Fig. 3). The patient has been followed 11½ years with no further difficulty.

The further growth of a carcinoma developing in the wall of a sebaceous cyst may be predominantly inward or outward into the adjacent tissues, and we have seen examples of both types of growth (Figs. 4 and 5). Puhr[10] found inward growth to be more common in cases collected from the literature and Stone and Abbey[3] note that the direction of growth, along with

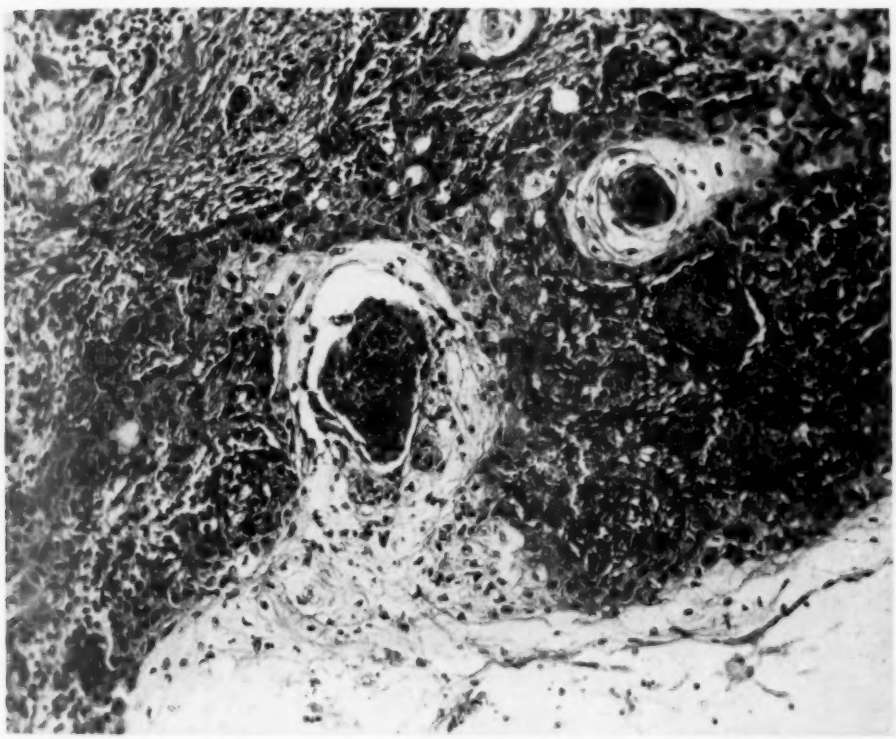


FIG. 5.—Case 2. Well-differentiated squamous cell carcinoma of wall of sebaceous cyst extending into stromal tissue and showing keratinization and pearl formation. (170x)

the differentiation of the tumor, may be of importance in the metastatic behavior of the carcinoma. Actually even regional lymph node metastases have been rare in the case reports of this type of cancer. Caylor,[2] Seff and Berkowitz[13] and Gregersen[15] report one case each with generalized metastases, the case of Gregersen metastasizing to the brain. Two of our cases showed regional node metastases, one described above the second briefly described here.

Case 2.—A 79-year-old white male entered Barnes Hospital complaining of a recurrent lesion of the right ear removed by cautery six weeks previously. The lesion of the ear was of 18 months duration. Many other face lesions of unknown character had been previously removed elsewhere. On examination the patient displayed a typical sailor's skin in addition to a crusted, ulcerated lesion of the right ear. The preoperative diagnosis was carcinoma, basal cell or squamous cell type. Histologic examination of the specimen showed a well-differentiated squamous cell carcinoma originating in the wall of a sebaceous cyst (Fig. 5).

Seven months later the patient returned with an ulcerated, indurated mass below the right ear about 5 centimeters in diameter and fixed to the deeper structures. This lesion could be only incompletely removed due to fixation to the transverse processes of the cervical vertebrae. Microscopic examination of this specimen showed a squamous cell carcinoma deep in the subcutaneous tissue. Lymphatic permeation was a prominent feature of the sections, particularly around nerves and one lymph node showed invasion by cancer (Fig. 6a and 6b).

Within the tissue adjacent to any sebaceous cyst one may, upon occasion, find evidence of a foreign body type of reaction, and this has been already mentioned as of some differential value in determining the origin of a carcinoma suspected of arising in a sebaceous cyst. This reaction to the fatty products of the cyst is made up of large mononuclear cells, some with a foamy cytoplasm due to phagocytized fat, collections of small round cells of the lymphocytic type, foreign body giant cells, and a marked fibrosis with cholesterol clefts (Fig. 1).

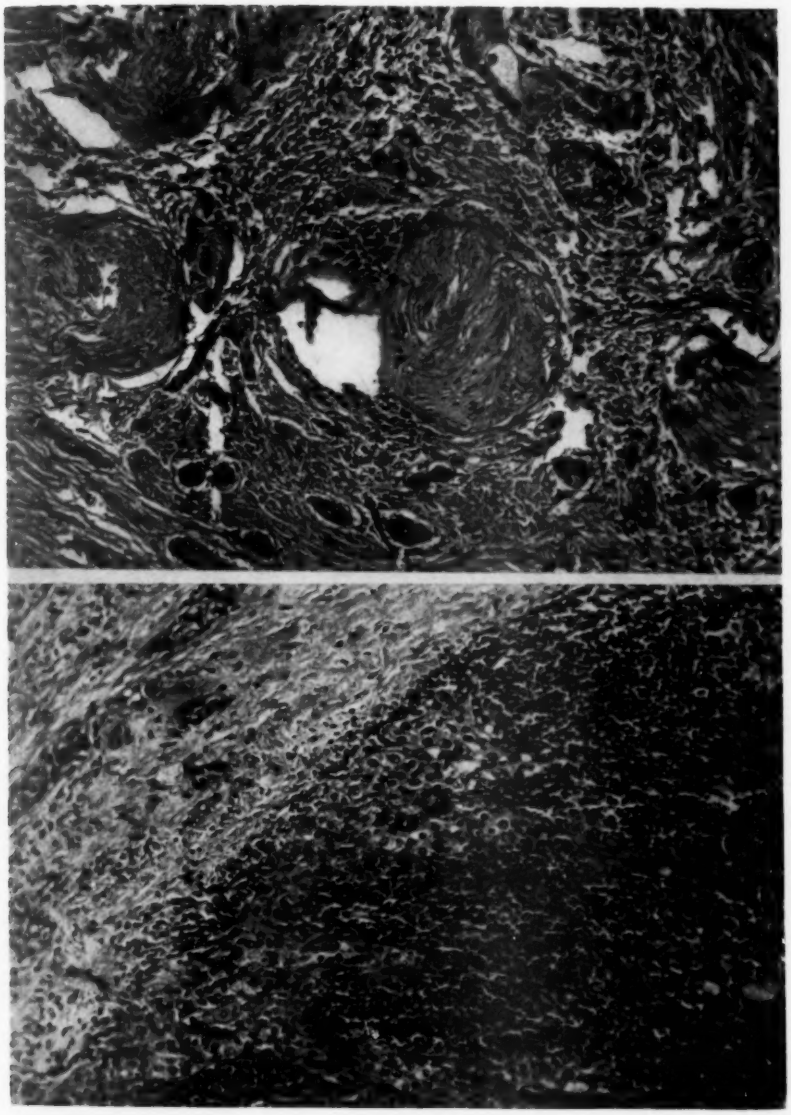
TREATMENT

It is not recommended that all sebaceous cysts be excised solely because of the possibility of malignant change, as this alteration is thought to be too rare to justify this treatment. Esthetic reasons constitute a more important indication for removal, and the development of a foreign body inflammatory reaction may lead to significant scarring and prevent easy excision. However, in an individual in the older age group who has an apparent sebaceous cyst of long standing, particularly on the face or scalp, with perhaps ulceration and particularly with some change in character such as an increase in size, a relatively wide excision is indicated because of the possibility of carcinomatous change. A prophylactic regional node dissection is in general not indicated as metastases are rare, but treatment should be individualized and in an extensive lesion of marked anaplasia immediate removal of the regional nodes may be considered. Evidence of regional node metastases subsequent to simple local excision should be treated by block excision of the lymph nodes.

PROGNOSIS

The prognosis in this tumor is good although recurrence may be expected if excision is not adequate, and adequate excision depends on a high degree of suspicion in presumed sebaceous cysts which demonstrate some of the characteristics emphasized above. It has been mentioned in the litera-

A



B

FIG. 6A.—Case 2. Perineural lymphatic permeation by metastatic squamous cell carcinoma. (145x).

B.—Case 2. Involvement of peripheral sinus of lymph node by metastatic squamous cell carcinoma. (145x).

ture[2, 3] that recurrence following excision of a sebaceous cyst should arouse one's suspicion regarding its possible malignant nature and indicate a further wide excision. With this we agree, but we believe that it is more important to emphasize the necessity for routine microscopic examination of all sebaceous cysts removed, a proposition that may well be followed for all tissues removed. If this is done, there will be no doubt concerning the proper treatment of recurrent lesions.

Bishop[1] knew of no deaths in his 11 cases; Collins[6] found two deaths in five cases of Grade III or IV and none in 14 cases of Grade I or II in material collected from individual series in which grading had been done. Caylor[2] had one known death with generalized metastases in 12 cases, and Seff and Berkowitz[13] and Gregersen[15] each had one death with generalized metastases. Our own follow-up reveals only one uncured patient who had unresectable lymph node metastases; nine patients are living and well, two and one-half to eleven and one-half years, and one patient died of unrelated cause and without recurrence five years after operation. Thus, ten of eleven patients with sufficient follow-up have been cured.

CONCLUSIONS

1. Fourteen cases of carcinoma were found in 832 sebaceous cysts removed, an incidence of 1.7 per cent. This incidence does not justify considering sebaceous cyst as a precancerous lesion.

2. However, in older patients who have had a sebaceous cyst of relatively long duration on the face or scalp, perhaps ulcerated, and in which a recent change in character such as an increase in size has been observed, carcinoma should be suspected.

3. The most common type of cancer found in sebaceous cysts is a well-differentiated squamous cell carcinoma of low grade malignancy, and these usually have not metastasized when first seen. Basal cell carcinomas occur much less frequently.

4. Sebaceous cysts which are suspected of fostering carcinoma should be treated by wide local excision; immediate lymph node dissection is not in general necessary although markedly anaplastic growths may justify such a procedure. Evidence of lymph node metastasis subsequent to previous local excision should be treated by block removal of the nodes.

5. With adequate treatment the prognosis is good. However, if routine histologic examination of all sebaceous cysts removed is not done, adequate treatment of a carcinoma may be delayed and a chance for cure may be lost.

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COMPARISON OF THE EFFICACY OF THERAPEUTIC AGENTS IN THE TREATMENT OF EXPERIMENTALLY INDUCED DIFFUSE PERITONITIS OF INTESTINAL ORIGIN*

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AN OPERATION DESIGNED TO PRODUCE a fulminating rapidly fatal peritonitis of intestinal origin was performed on 111 dogs. It was necessary to exclude 18 animals from the group because of complications that interfered with the experiments such as death from anesthesia, air embolism during intravenous therapy, internal fecal fistula, appendiceal avulsion, and hemorrhage. The remaining 93 animals were considered satisfactory for the purpose of evaluating therapeutic agents for the treatment of experimental peritonitis of appendiceal origin.

METHOD

A method that had previously been developed in this laboratory was used. Laparotomy was performed under sodium pentobarbital anesthesia; the blood supply to the appendix was divided and ligated; feces was expressed into the appendix, filling its lumen completely; the base of the appendix was ligated with flat cotton tape ¼ inch in width; the appendix was crushed by clamping it repeatedly with a large Kocher type hemostat; the spleen and omentum were removed; the animal was given 60 cc. of castor oil by gavage. A small soft rubber tube was placed in the peritoneal cavity and brought out through the laparotomy incision. With the use of aseptic precautions peritoneal fluid for bacterial cultures was aspirated through this tube which was then removed. (Preliminary sampling experiments had revealed definite gross evidence of peritonitis and positive bacterial cultures to be uniformly present six hours after operation.)

The tube also served in some experiments as the means for introducing intraperitoneal therapy. In such experiments, the tube was left in place until the intraperitoneal therapy was discontinued. At the time the tube was removed the skin and subcutaneous tissues were sutured to prevent leakage of peritoneal fluid through the wound. In most of the animals the tubes functioned satisfactorily, but occasionally an animal would withdraw the tube before the experiment was completed.

Simultaneous determinations of blood and peritoneal fluid levels of chemotherapeutic agents were made in some experiments in order to determine

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concentrations and blood-peritoneal fluid relationships during the period of treatment of the infection. The dosage and method of administration of the various chemotherapeutic agents used are described separately with each group of experiments. All experimental animals were given parenteral fluids postoperatively to maintain adequate water and electrolyte intake.

Temperature recordings and leucocyte counts were made in the early experiments but were not done later as they usually were found to be elevated above normal, and this fact did not contribute significantly to the experiment. The appearance, illness, toxicity, and the behavior and habitus of the animals were found to be more valuable indications of the progress of the infection.

Autopsies with bacteriologic and pathologic studies were done at once on all animals that died. Laparotomies with bacteriologic and pathologic studies were performed at weekly intervals on all surviving animals.

CONTROLS

Twenty animals served as controls. All became acutely ill, vomited, grew progressively lethargic and toxic, became comatose and died. The average

TABLE I.—*Experimental Peritonitis*

Untreated Control Series (20 animals) Organisms Cultured	Number of Animals	
Escherichia coli	19	
Proteus vulgaris	2	
Bacterioides	2	
Aerobic sporeforming bacilli	1	
Clostridia	15	
Alpha hemolytic streptococcus	3	16
Beta hemolytic streptococcus	5	
Streptococcus fecalis	8	
Hemolytic *staphylococcus aureus*	1	10
Nonhemolytic *staphylococcus albus*	6	
Hemolytic *staphylococcus albus*	3	

survival period was 39 hours. Autopsies revealed a diffuse acute inflammatory process throughout the peritoneum. The peritoneal cavity contained thin sanguineous exudate estimated at from 100 cc. to 1000 cc. Varying amounts of fibrinous exudate were deposited about the peritoneal cavity. The appendix was covered with yellow-green exudate and there was no evidence of localization or of a "walling off" process about the appendix.

The bacteria cultured from peritoneal fluid in the untreated control animals are listed in Table I. The organisms most often found were Clostridia, Streptococci and *Escherichia coli.*

GROUP I. INTRAVENOUS SODIUM SULFADIAZINE

Five dogs in which appendiceal peritonitis had been produced were treated with intravenous sodium sulfadiazine. Therapy was started six hours post-

operatively. Each animal received 4.0 Gm. of sodium sulfadiazine twice daily with Sodium R Lactate 1/6 M to maintain an alkaline reaction in the urine. There was no apparent beneficial effect from sodium sulfadiazine therapy. The progress of the infection was identical with that in untreated control animals. All died. The average survival period was 44 hours. Table II indicates the types of organisms cultured before therapy and at autopsy.

TABLE II.—*Experimental Peritonitis*

Group I. 5 animals.

Sodium sulfadiazine 4.0 Gm. given twice daily, intravenously

Organisms Cultured	Incidence: 6 Hrs. Postop. (3 Dogs)	Incidence: Necropsy (5 Dogs)
Escherichia coli	1	4
Proteus vulgaris	0	2
Aerobic sporeforming bacillus	1	0
Clostridia	2	5
Alpha hemolytic streptococcus	0	2
Streptococcus fecalis	0	3
Beta hemolytic streptococcus	0	1
Gamma streptococcus	1	0
Nonhemolytic *staphylococcus albus*	0	2
Hemolytic *staphylococcus albus*	1	0

TABLE III.—*Experimental Peritonitis*

Group I.

Blood and peritoneal fluid sulfadiazine levels (milligrams per cent) following the administration of 4.0 Gm. of sodium sulfadiazine intravenously

Hours	Blood	Peritoneal Fluid
0	0	0
2	24.0	24.0
4	23.0	23.0
6	23.0	23.0
8	23.0	23.0

TABLE IV.—*In vitro Sulfadiazine Susceptibility*

Group I.

Organisms Cultured	Milligrams Per Cent
Escherichia coli	8
Proteus vulgaris	8
Alpha hemolytic streptococcus—Not susceptible to	10
Beta hemolytic streptococcus	8
Gamma streptococcus	8
Streptococcus fecalis	Not susceptible
Clostridia	
Hemolytic *staphylococcus albus*	8
Nonhemolytic *staphylococcus albus*	8

The concentrations of sulfadiazine in the blood and peritoneal fluid in this group are shown in Table III.

Table IV indicates the *in vitro* sulfadiazine susceptibility of the individual organisms cultured from these experiments.

GROUP II. INTRAPERITONEAL SULFANILAMIDE COMBINED WITH INTRAVENOUS SULFADIAZINE

Five dogs in which appendiceal peritonitis had been produced were treated with intravenous sulfadiazine therapy exactly as described in the preceding group of experiments. In addition, 5.0 Gm. of sulfanilamide were given intraperitoneally through the rubber tube six hours postoperatively just prior to removal of the tube.

Table V shows the blood sulfanilamide concentration following the intraperitoneal instillation of 5.0 Gm. of sulfanilamide.

TABLE V.—*Experimental Peritonitis*
Group II.

Blood sulfanilamide levels following intraperitoneal instillation of 5.0 Gm. of sulfanilamide

Time	Blood Level (mg. %)
0	0
15 minutes	6.20
1½ hours	14.05
4 hours	15.35
6 hours	13.29
8 hours	15.50
24 hours	6.78

Although the survival period was prolonged in this group (average 80 hours) all animals died. The course of illness and the pathological findings were similar to the untreated controls.

The types of organisms cultured are shown in Table VI. Sulfadiazine mixed culture tests showed most of these organisms to be resistant to sulfadiazine in concentrations up to 12,500 mg. per cent, and sulfanilamide mixed culture tests showed all organisms to be resistant to concentrations of sulfanilamide up to 200 mg. per cent.

TABLE VI.—*Experimental Peritonitis*
Group II. 5 animals.

Sodium sulfadiazine intravenously, 4.0 Gm. twice daily, and sulfanilamide, 5.0 Gm. six hours post-operatively, intraperitoneally

Organisms Cultured	Incidence: 6 Hrs. Postop. (5 Dogs)	Incidence: Necropsy (5 Dogs)
Escherichia coli	1	4
Clostridia	1	3
Streptococcus fecalis	4	5
Hemolytic *staphylococcus aureus*	2	1
Hemolytic *staphylococcus albus*	2	3
Hemolytic *staphylococcus citrous*	1	0
Diphtheroids	2	0
Aerophilic lactobacilli	0	2

At autopsy peritoneal fluid sulfadiazine levels were found to vary from 44.0 to 182.0 mg. per cent.

GROUP III. INTRAPERITONEAL SULFASUXIDINE

Five dogs in which experimental appendiceal peritonitis had been produced were treated with intraperitoneal instillations of sulfasuxidine (1.0 Gm. per kilogram of body weight) once daily beginning six hours postoperatively. All animals died. The course of illness, period of survival (average 40 hours) and necropsy findings were similar in every respect to the untreated control series.

Table VII shows the bacteriology in this group of experiments.

TABLE VII.—*Experimental Peritonitis*
Group III. 5 animals.

Sulfasuxidine 1.0 Gm. per kg. per day intraperitoneally			
	Incidence		
Organisms Cultured	6 Hrs. Postop. (5 dogs)	1 Day Postop. (2 dogs)	Necropsy (5 dogs)
Escherichia coli	2	1	5
Proteus vulgaris	..	1	..
Clostridia	3	1	2
Streptococcus fecalis	4	2	3
Staphylococcus aureus	2	0	0
Staphylococcus albus	2	0	1
Diphtheroids	..	..	1

Undissolved sulfasuxidine varying from small to considerable amounts was found spread throughout the peritoneal cavity at autopsy. Occasionally considerable accumulations of the drug were found to be pocketed in fibrin. The concentration of sulfasuxidine in the peritoneal fluid at autopsy was found to be from 6.0 to 42.0 mg. per cent (measured as sulfathiazol). Table VIII shows increasing sulfasuxidine resistance of the bacterial flora and the concentration of the drug in these experiments.

TABLE VIII.—*Sulfasuxidine Susceptibility Tests*
Group III.

	6 Hours Postoperatively	Necropsy
Escherichia coli	Susceptible 3.12–6.24 mg.%	Most susceptible at 50.0 mg.%
Proteus vulgaris		Not susceptible at 50.0 mg.%
Clostridia	Susceptible 0.28–50.0 mg.%	Not susceptible at 50.0 mg.%
Streptococcus fecalis	Most unsusceptible to 50.0 mg.%	Some not susceptible and some susceptible to 50.0 mg.%
Staphylococcus aureus	Susceptible 0.25–50.0 mg.%	Not susceptible at 50.0 mg.%
Diphtheroids		Not susceptible at 50.0 mg.%

GROUP IV. STREPTOMYCIN
(INTRAMUSCULARLY BEGINNING SIX HOURS POSTOPERATIVELY)

Ten dogs in which appendiceal peritonitis had been produced were treated with intramuscular injections of streptomycin. Therapy was started six hours postoperatively. Each animal received 2 Gm. of streptomycin daily in divided

doses of .33 Gm. given intramuscularly at four-hour intervals. Two of the ten animals recovered from the acute peritonitis under streptomycin therapy, but a fecal fistula suddenly developed in one of the animals on the sixth postoperative day and it expired the following day. The remaining eight animals died with the same acute signs of peritonitis as the controls, but their average survival period was 92 hours, as compared to an average survival period of 39 hours for the untreated control animals. The only pathogenic organisms that were consistently susceptible to the streptomycin in vitro were *Escherichia coli* and they usually persisted in their growth in vivo and were found at autopsy. The Streptococci and Clostridia were uniformly resistant to streptomycin both in vitro and in vivo.

TABLE IX.—*Experimental Peritonitis*
Group IV. 10 animals.

Streptomycin 2.0 Gm. daily (.33 Gm. intramuscularly every 4 hours). Started 6 hours postoperatively

Organisms Cultured	Incidence: 6 Hrs. Postop. (7 dogs)	Incidence: Necropsy (9 dogs)
Escherichia coli	6	9
Proteus vulgaris	0	1
Bacterioides	1	0
Aerobic sporeforming bacillus	1	1
Clostridia	5	8
Alpha hemolytic streptococcus	1	1
Beta hemolytic streptococcus	2	4
Gamma streptococcus	2	1
Streptoccus fecalis	1	2
Nonhemolytic *staphylococcus albus*	2	2
Hemolytic *staphylococcus albus*	1	1
Hemolytic *staphylococcus aureus*	1	1

The one streptomycin-treated animal that survived without complications was lost inadvertently during induction of anesthesia prior to exploratory laparotomy on the seventh postoperative day. Gross examination of the peritoneal cavity revealed evidence of subsiding peritonitis. Cultures of the peritoneal exudate taken before the streptomycin therapy was started grew the usual bacterial flora of the colon.

Table IX shows the types of organisms cultured from the animals in this experiment.

Table X gives the streptomycin susceptibility of the bacterial organisms cultured from the peritoneal cavity prior to treatment of this group of animals with streptomycin.

Table XI shows blood and peritoneal fluid streptomycin concentrations following intramuscular administration of streptomycin.

GROUP V. STREPTOMYCIN (INTRAMUSCULARY BEGINNING IMMEDIATELY POSTOPERATIVELY)

Five dogs in which appendiceal peritonitis had been produced were treated with streptomycin beginning immediately after operation. Each animal was

given 2 Gm. of streptomycin daily in divided doses of .33 Gm. intramuscularly every four hours. The course of infection in these animals was similar to that in the untreated control animals. All died. However, the average survival period of these animals treated with streptomycin was 75 hours as compared with an average survival period of 39 hours for the untreated control animals.

Table XII indicates the bacteria cultured in this group of experiments.

TABLE X.—*Experimental Peritonitis*
Group IV.

Organisms	Streptomycin susceptibility Units per Cubic Centimeter
Escherichia coli	1.78–20.0
Proteus vulgaris	7.1 –80.0
Bacterioides	Not susceptible
Aerobic sporeforming bacillus	3.0
Pseudomonas aeruginosa	Not susceptible
Clostridia	Not susceptible
Alpha hemolytic streptococcus	Not susceptible
Beta hemolytic streptococcus	1.3 –28.5
Gamma streptococcus	3.57
Streptococcus fecalis	Not susceptible
Non hemolytic *staphylococcus albus*	14.6
Hemolytic *staphylococcus albus*	3.0 – 8.0
Hemolytic *staphylococcus aureus*	2.0

TABLE XI.—*Experimental Peritonitis*
Group IV.

Blood and peritoneal fluid streptomycin concentrations (units per cubic centimeter) following the administration of 0.33 Gm. of streptomycin intramuscularly

Hours	Blood	Peritoneal Fluid
0	0	0
1	20	0
2	40	20
3	40	20
4	20	10

TABLE XII.—*Experimental Peritonitis*
Group V. 5 animals.

Streptomycin 2.0 Gm. daily (.33 Gm. intramuscularly every 4 hours) beginning immediately after completion of operation

Organisms Cultured	Incidence 6 Hrs. Postop. (4 dogs)	Necropsy (5 dogs)
Escherichia coli	2	3
Bacterioides	0	1
Clostridia	3	4
Alpha hemolytic streptococcus	0	1
Beta hemolytic streptococcus	1	0
Gamma streptococcus	1	0
Streptococcus fecalis	2	3
Nonhemolytic *staphylococcus albus*	2	0
Nonhemolytic *staphylococcus aureus*	1	0
Diphtheroid bacillus	2	0

GROUP VI. STREPTOMYCIN INTRAPERITONEALLY

Ten dogs in which peritonitis was produced were treated with intraperitoneal instillation of streptomycin. Therapy was started six hours postoperatively.

A. In the first group of five animals, three were given 0.4 Gm. intraperitoneally on two occasions on the day of operation, and 0.4 Gm. daily thereafter. Two animals were given 0.8 Gm. twice daily on the day of operation, and 0.8 Gm. once daily thereafter. All animals died with acute peritonitis. The course of illness and autopsy findings were the same as those in the untreated control animals. However, the average survival period of the animals treated with intraperitoneal streptomycin was 87 hours compared with an average survival period of 39 hours for the untreated controls.

Table XIII shows the bacteriologic findings six hours postoperatively and at necropsy in this group of experiments. Additional cultures taken at 22, 30, 48 and 72 hours postoperatively were similar to those made at necropsies.

TABLE XIII.—*Experimental Peritonitis*
Group VI-A 5 animals.

Streptomycin intraperitoneally 0.4 to 1.6 Gm. daily	Incidence	
Organisms Cultured	6 Hrs. Postop. (4 dogs)	Necropsy (5 dogs)
Escherichia coli	2	4
Clostridia	3	5
Alpha hemolytic streptococcus	2	4
Gamma streptococcus	0	1
Streptococcus fecalis	1	0
Nonhemolytic *staphylococcus albus*	2	1

B. Up to this point in vitro laboratory tests and animal experiments had demonstrated considerable evidence that the pathogenic bacterial flora of experimental peritonitis were resistant to streptomycin in concentrations and doses that ordinarily would be considered safe to use in therapy of human patients. It was decided to attempt to use intraperitoneally doses of streptomycin that would be more likely (based on in vitro streptomycin susceptibility tests) completely to destroy all pathogenic organisms. Four (4.0) Gm. of streptomycin were instilled intraperitoneally in each of five dogs six hours after completion of the operation to produce experimental peritonitis. All dogs died within 10 to 30 minutes after either their first or second instillation of streptomycin. The average survival period was 12 hours. These deaths occurred from respiratory failure due to the toxic effect of streptomycin on the medullary centers. Blood streptomycin concentration was 160 units per cc. 10 minutes after intraperitoneal instillation of 4.0 Gm. of streptomycin.

Bacterial cultures of the peritoneal fluid were taken at necropsy in four of the animals in this group. In three animals the cultures were sterile. Escherichia coli and Clostridia were cultured from the peritoneal fluid

specimen taken at the necropsy of the fourth animal. All animals had gross evidence of acute diffuse peritonitis at autopsy.

Table XIV indicates the bacteriologic findings in this group of experiments.

TABLE XIV.—*Experimental Peritonitis*
Group VI-B 5 animals.

Streptomycin intraperitoneally 4.0 Gm. twice daily beginning 6 hours postoperatively

Organisms Cultured	Incidence	
	6 Hrs. Postop. (4 dogs)	Necropsy (4 dogs)
Escherichia coli	3	1
Clostridia	3	1
Alpha hemolytic streptococcus	2	0
Beta hemolytic streptococcus	1	0
Gamma streptococcus	1	0
Hemolytic *staphylococcus aureus*	1	0

GROUP VII. PENICILLIN

Commercially available penicillin was given intramuscularly in divided doses every four hours to three groups of animals. Penicillin therapy was started six hours following operations for the production of experimental peritonitis of appendiceal origin. Each animal in the first group received 100,000 units of penicillin per day, the second group 200,000 units of penicillin per day, and the third group 500,000 units of penicillin per day. All animals that survived received treatment for six days.

A. One out of three animals in the first group (treated with 100,000 units of penicillin daily for six days) survived and two died with diffuse peritonitis. The course of illness, pathology and bacteriologic cultures in the animals that died were similar to those seen in the untreated control animals. The one animal that survived had gross pathologic evidence of a subsiding peritonitis when examined at exploratory laparotomy on the seventh day. Bacteriologic cultures made on that day grew Gamma streptococci and Clostridia. Apparently the laparotomy reactivated the infection for the animal died five days later with acute diffuse peritonitis (no attempt was made to treat this animal with penicillin following the exploratory laparotomy).

B. In the second group (treated with 200,000 units of penicillin daily for six days) two animals survived and three died with acute diffuse peritonitis. The course of the disease, pathologic and bacteriologic findings in the animals that died were similar to those in the untreated control series. The animals that survived had positive bacterial cultures and gross evidence of subsiding acute peritonitis at exploratory laparotomies performed on the seventh day. One survivor died four days after exploratory laparotomy with fulminating diffuse peritonitis. The other survivor was examined at necropsy one month postoperatively (during this period of one month the animal appeared and

behaved like a normal healthy dog) at which time the peritoneal cavity contained a slightly increased amount of peritoneal fluid and minute scattered granulations over parietal and visceral peritoneum and the cultures grew *Escherichia coli.*

C. All the animals in the third group (treated with 500,000 units of penicillin daily for six days) survived the acute phase of experimentally induced peritonitis. At first they were acutely ill, but soon all evidence of toxicity and illness disappeared. Exploratory laparotomies performed on the seventh postoperative day revealed evidence of subsiding peritonitis, and bacterial cultures grew a mixed bacterial flora. One animal died with fulminating acute diffuse peritonitis due to reactivation of the infection at the exploratory laparotomy on the seventh day. The other four animals were examined again at laparotomy on the 30th day when positive bacterial cultures were obtained in three dogs and all had scattered pin point size granulations throughout the peritoneum. One animal was apparently healthy for two months postoperatively, then acute diffuse peritonitis developed (pure culture of *Escherichia coli*) with extensive exudation and necrosis, and the animal died.

Two months postoperatively exploratory laparotomies on the remaining survivors still revealed minute scattered granulations, but the bacterial cultures were sterile. The results are summarized in the following table:

TABLE XV.—*Experimental Peritonitis*
Group VII. 13 animals.

Penicillin (commercial) given intramuscularly in divided doses every 4 hours				
Group	Daily Penicillin Dosage (units)	Number of Dogs	Recovered	Died
A.	100,000	3	1	2
B.	200,000	5	2	3
C.	500,000	5	5*	0

* One dog died with Escherichia coli peritonitis two months after treatment.

Table XVI shows the bacteriology in these groups of animals treated with commercial penicillin.

Table XVII shows blood and peritoneal fluid concentrations following the administration of 16,667 units of commercially available penicillin intramuscularly.

GROUP VIII. PENICILLIN AND STREPTOMYCIN THERAPY COMBINED

Five animals in which peritonitis of appendiceal origin was produced were treated with penicillin and streptomycin for six days, beginning six hours postoperatively. Each animal received 500,000 units of penicillin and 2.4 Gm. of streptomycin daily in divided doses, given at four-hour intervals by intramuscular administration. All five animals in this group survived. The findings were almost identical to those in the animals of Group VII-C which were treated with 500,000 units of penicillin daily.

TABLE XVI.—*Experimental Peritonitis*
Group VII.

Bacteriology—commercial penicillin series

Group A. 100,000 Units Daily	6 Hours (3 dogs)	7 Days (1 dog)	Necropsy (2 dogs)
Escherichia coli	3	0	2
Pseudomonas aeruginosa	0	0	1
Bacterioides	0	0	1
Clostridia	3	1	2
Alpha streptococcus	3	0	2
Beta streptococcus	1	0	2
Gamma streptococcus	1	1	1
Streptococcus fecalis	0	0	1

Group B. 200,000 Units Daily	6 Hours (5 dogs)	7 Days (2 dogs)	30 Days 1 dog)	Necropsy (4 dogs)
Escherichia coli	2	1	1	2
Clostridia	5	2	0	3
Alpha hemolytic streptococcus	0	0	0	1
Beta hemolytic streptococcus	1	0	0	1
Streptococcus fecalis	4	2	0	3
Staphylococcus albus	1	0	0	0
Staphylococcus aureus	1	0	0	0

Group C. 500,000 Units Daily	6 Hours (5 dogs)	7 Days (5 dogs)	30 Days (4 dogs)	Necropsy (60 days 1 dog)
Escherichia coli	1	5	3	1
Aerobacter aerogenes	0	3	0	0
Clostridia	2	5	2	0
Streptococcus fecalis	0	4	1	0
Beta hemolytic streptococcus	1	0	0	0
Gamma streptococcus	1	0	0	0
Staphylococcus aureus	1	0	0	0

TABLE XVII.—*Experimental Peritonitis*
Group VII.

Blood and peritoneal fluid concentrations of penicillin (units per cubic centimeter) following intramuscular injection of 16,667 units of penicillin

Hours	Blood	Peritoneal Fluid
0	0	0
1	1.20	0.62
2	2.50	1.20
3	0.62	0.31
4	0.15	0.31

TABLE XVIII.—*Experimental Peritonitis*
Group VIII. 5 animals.

Penicillin (500,000 units daily) and Streptomycin (2.4 Gm. daily) given intramuscularly in divided doses at 4 hour intervals

Organisms Cultured	Incidence		
	6 Hours (4 dogs)	7 Days (5 dogs)	28 Days (1 dog)
Escherichia coli	1	3	0
Clostridia	3	4	1
Streptococcus fecalis	0	3	1
Nonhemolytic *staphylococcus albus*	1	1	1
Diphtheroid bacillus	1	0	0

Table XVIII shows organisms cultured in this group of experiments.

Table XIX shows penicillin and streptomycin susceptibility of organisms cultured before therapy, and after seven days of therapy with streptomycin and penicillin.

TABLE XIX.—*Experimental Peritonitis*
Group VIII.

Bacterial susceptibility tests. Cultures made from animals receiving penicillin and streptomycin therapy (Units per cubic centimeter)

Organisms Cultured	6 Hours		7 Days	
	Penicillin	Streptomycin	Penicillin	Streptomycin
Escherichia coli	25.0	35.0	–200.0	300–600.0
Clostridia	0.57	1.05	12.5–100.0	17.25–300.0
Streptococcus fecalis	0.028	0.05	13.12– 50.0	9.3 –150.0
Nonhemolytic *staphylococcus albus*	0.57	1.05		

GROUP IX. PENICILLIN-X (INTRAMUSCULAR)

Penicillin containing 15 to 25 per cent penicillin-x was given to a group of ten animals in which experimental peritonitis of appendiceal origin had been produced. Treatment was started six hours after the surgical procedure to produce peritonitis. The penicillin-x was given intramuscularly in divided doses at four-hour intervals. A total dosage of 100,000 units a day for six days was given each animal. Nine animals survived and one expired after living 76 hours after the onset of peritonitis. All survivors recovered very rapidly from the initial acute illness on penicillin-x therapy. Recovery from toxicity and lethargy occurred very early, and normal appetite and activity were observed during the first few days of treatment in these animals.

Bacteriologic cultures made from the peritoneal fluid from the animal that died grew Escherichia coli, *Proteus vulgaris,* Bacterioides and an aerobic spore-forming Bacillus, all relatively resistant to penicillin-x. Exploratory laparotomies performed seven days postoperatively on the survivors showed evidence of a subsiding acute peritonitis, and bacterial cultures made at that time grew penicillin-resistant gram negative flora, Clostridia (3 animals) and a penicillin resistant *streptococcus fecalis* (1 animal).

Exploratory laparotomies performed 30 days later revealed no evidence of the peritonitis and all bacterial cultures made at this time were sterile.

Table XX indicates the blood and peritoneal fluid concentrations of penicillin following intramuscular administration of penicillin-x.

Table XXI gives the results and bacteriologic findings in this group of experiments.

GROUP X. PENICILLIN-X (INTRAPERITONEAL)

Five dogs in which experimental appendiceal peritonitis had been produced were treated with intraperitoneal instillations of penicillin containing 15 to 25 per cent penicillin-x, beginning six hours postoperatively. Each animal received 100,000 units of penicillin (with 15 to 25 per cent penicillin-x) twice

the first day, and 100,000 units daily thereafter for six days. Two animals survived and three died. One died during the course of therapy, one died immediately after the cessation of therapy, and the third animal died several days after the completion of therapy.

TABLE XX.—*Experimental Peritonitis*
Group IX.

Blood and peritoneal fluid concentrations of penicillin (units per cubic centimeter) following intramuscular injections of 16,667 units of penicillin containing 15 to 25 per cent penicillin-x

Hours	Blood	Peritoneal Fluid
0	0	0
1	2.50	1.20
2	2.50	0.62
3	2.50	0.62
4	0.31	0.62

Necropsy in the three fatal cases showed a diffuse peritonitis, and bacteriologic cultures grew the usual mixed flora from the colon. The animals that died were acutely ill and toxic. The two animals that survived were examined by exploratory laparotomy two weeks and four weeks postoperatively. Diffuse, extensive granulations up to ¼ inch in thickness were found throughout the peritoneal cavities of these two animals and bacterial cultures revealed persistence of the pathogenic organisms. These two animals were

TABLE XXI.—*Experimental Peritonitis*
Group IX. 10 animals.

Penicillin (15 to 25 per cent pencillin-x) intramuscularly, 100,000 units daily (16,667 units every 4 hours) for 6 days

Organisms Cultured	Incidence		
	6 Hrs. Postop. (8 dogs)	7 Days (9 dogs)	30 Days 5 dogs)
Escherichia coli	6	5	0
Proteus vulgaris	1	2	0
Aerobacter aerogenes	0	1	0
Pseudomonas aeruginosa	0	1	0
Aerobic sporeforming bacillus	0	1	0
Clostridia	8	3	0
Alpha hemolytic streptococcus	5	0	0
Beta hemolytic streptococcus	2	0	0
Streptococcus fecalis	0	1	0
Nonhemolytic *staphylococcus albus*	4	0	0
Hemolytic *staphylococcus albus*	2	0	0
D phtheroid bacillus	1	0	0

acutely ill at the onset of the peritonitis, but signs of toxicity rapidly decreased during intraperitoneal penicillin therapy and their appearance and behavior seemed entirely normal at the time of the follow-up exploratory procedures.

Table XXII shows the results and the bacterial cultures in this group of experiments. There was no alteration of penicillin susceptibility in the bacteria during the course of intraperitoneal therapy with penicillin-x.

Table XXIII shows blood and peritoneal fluid penicillin levels in this group of experiments.

SUMMARY

Table XXIV summarizes the results of these experiments in the treatment of peritonitis of appendiceal origin in dogs with sulfonamides and antibiotics.

TABLE XXII.—*Experimental Peritonitis*
Group X. 5 animals.

Penicillin (15 to 25 per cent penicillin-x) 100,000 units intraperitoneally daily for 6 days

Organisms Cultured	Incidence			
	6 Hours Postop. (8 dogs)	Necropsy (3 dogs)	15 Days (2 dogs)	30 Days (2 dogs)
Escherichia coli	5	3	2	2
Proteus vulgaris	2	1	0	0
Clostridia	5	3	2	2
Alpha hemolytic streptococcus	3	2	0	2
Beta hemolytic streptococcus	2	2	2	1
Gamma streptococcus	1	0	0	0
Streptococcus fecalis	1	0	1	0
Nonhemolytic *staphylococcus albus*	1	0	2	0
Hemolytic *staphylococcus albus*	2	2	0	0
Hemolytic *staphylococcus aureus*	2	0	0	0
Diphtheroid bacillus	1	0	0	0

TABLE XXIII.—*Experimental Peritonitis*
Group X.

Blood and peritoneal fluid concentrations of penicillin (units per cubic centimeter) following the intraperitoneal instillation of 100,000 units of penicillin (15 to 25 per cent penicillin-x)

Hours	Blood	Peritoneal Fluid
0	0	0
1	19.96	80.00
2	9.95	80.00
3	4.99	9.95
4	1.20	4.99
10	.....	0

CONCLUSION

Fulminating diffuse peritonitis was produced in 93 dogs by dividing the vascular supply to the appendix; ligating the base, and crushing the appendix. The omentum and spleen were removed. Twenty untreated control animals died with acute diffuse peritonitis from bacterial infection with intestinal organisms. The average survival period was 39 hours.

Sulfonamide therapy with (1) intravenous sodium sulfadiazine (5 dogs), (2) intraperitoneal sulfasuxidine (5 dogs), and (3) combined intraperitoneal sulfanilamide and intravenous sodium sulfadiazine (5 dogs) apparently had no beneficial effect. All died with peritonitis similar to that observed in the control animals. However, the survival period in the sulfanilamide-sulfadiazine group was prolonged to 80 hours.

Streptomycin therapy given intramuscularly (10 dogs) and intraperitoneally (5 dogs) apparently prolonged the survival period of dogs with experimental appendiceal peritonitis to averages of 75 to 92 hours in 14 out of 15 dogs. One animal survived. However, doses of streptomycin that effectively controlled the organisms in the peritoneal cavity caused death from the toxic effect of streptomycin (apparently on the medullary respiratory center).

Commercially available penicillin given intramuscularly at four-hour intervals daily in doses of 100,000 units (3 dogs) 200,000 units (5 dogs) 500,000 units (5 dogs), and 500,000 units combined with streptomycin 2.4 Gm. was definitely beneficial in the treatment of experimental appendiceal peritonitis. All animals receiving 500,000 units of penicillin daily survived.

TABLE XXIV.—*Comparison of Therapeutic Agents for the Treatment of Experimental Peritonitis of Appendiceal Origin.*

	*Treatment	Number of Dogs	Recovered	Died	Average Survival Hours
	Controls—untreated	20	0	20	39
1.	Sulfadiazine 4 Gm. twice daily intravenously	5	0	5	44
2.	Sulfadiazine 4 Gm. twice daily intravenously and Sulfanilamide 5 Gm. intraperitoneally	5	0	5	80
3.	Sulfasuxidine intraperitoneally 1.0 Gm. per kilogram of body weight daily	5	0	5	40
4.	Streptomycin intramuscularly, 2.0 Gm. daily (started 6 hours postoperatively)	10	1	9	92
5.	Streptomycin intramuscularly, 2.0 Gm. daily (started immediately postoperatively)	5	0	5	75
6-A.	Streptomycin intraperitoneally 0.4 to 1.6 Gm. daily	5	0	5	87
6-B.	Streptomycin intraperitoneally 4.0 Gm. daily	5	0	5	12
7-A.	Penicillin intramuscularly 100,000 units daily	3	1	2	37
7-B.	Penicillin intramuscularly 200,000 units daily	5	2	3	65
7-C.	Penicillin intramuscularly 500,000 units daily	5	5	0	..
8.	Penicillin intramuscularly 500,000 units daily, and Streptomycin intramuscularly 2.4 Gm. daily	5	5	0	..
9.	Penicillin-x (15 to 25 per cent) intramuscularly 100,000 units daily	10	9	1	76
10.	Penicillin-x (15 to 25 per cent) intraperitoneally 100,000 units daily	5	2	3	135

* All therapy was begun 6 hours postoperatively unless otherwise specifically designated. All intramuscular therapy was given in equally divided doses at four-hour intervals.

Penicillin containing 15 to 25 per cent penicillin-x in doses of 100,000 units daily intramuscularly (10 dogs), and intraperitoneally (5 dogs) was effective in the treatment of experimental appendiceal peritonitis. Nine out of 10 animals treated intramuscularly, and 2 out of 5 animals treated intraperitoneally with penicillin-x recovered.

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GIANT CELL TUMOR OF THE SACRUM: A CASE REPORT*†

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CASE HISTORY

This 29-year-old white male was admitted to the hospital November 7, 1945. In April, 1945, he fell from a truck in England. No pertinent injury was sustained, but one week later there appeared pain in the lower back in the sacral region. One month later he noticed slight swelling in that region. Patient has not noted exaggeration of the pain by motion of the trunk, but states it is accentuated by prolonged sitting. During the past 3 to 4 months he has noted numbness in the posterior aspect of the left leg. There has been approximately 40 pounds weight loss with illness.

Roentgenograms taken on September 15, 1945, revealed a marked osteolytic process involving the distal four sacral segments and the coccyx. It was noted that the neoplasm had broken through the cortices in numerous places and had infiltrated the pre- and post-sacral soft tissues, resulting in a grapefruit-sized mass, most of which was in the pelvis.

Physical examination revealed a well-developed, undernourished, white male in no distress. Findings are limited to lower back and rectum. There is a large ovoid pulsating swelling which is located centrally in the region of the sacrum. Over the mass are many dilated blood vessels. Slight tenderness to palpation is present. Motion of the back does not accentuate the discomfort. Knee jerks are hyperactive bilaterally with absent ankle jerks. Area of hypesthesia involves the posterior aspect of the left thigh. Heart and lungs are normal.

Rectal examination reveals a protrusion of the sacral mass against the rectal wall which displaces the rectum anteriorly. Pulsation can be felt by examining finger. The outline is smooth, edge circumscribed, and no invasive tendencies are noted. Auscultation reveals no bruit. There is no thrill. Blood pressure: 130/80. R.B.C.: 4,350,000. Hemoglobin: 85 per cent. W.B.C.: 7,400. Coagulation time: 3 minutes. Bleeding time: 1½ minutes. Urine: negative.

Roentgen-ray report: The entire sacrum with the exception of its proximal end is destroyed, replaced and expanded in all diameters with a thin shell of subperiosteal new bone remaining irregularly distributed over the surface of the tumor and a few strands of bone remaining with it. The coccyx is partially destroyed.

DISCUSSION

Differential diagnosis involved consideration of either a pulsating tumor or aneurysm. Aneurysm could be readily eliminated because of the position where its presence would be rare, the fact that there was no thrill, bruit, or murmur, and the presence of the bony lacework in the tumor as viewed by roentgen-ray. The type of pulsation was definitely expansile. The question naturally arose as to whether or not the pulsation was a transmitted one. Rectal examination with bimanual palpation revealed the extent of pulsation

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to be the same, as near as one could tell, in the intrapelvic portion of the mass as in that portion located just beneath the skin. Finally, there was no history of the usual etiologic factors such as significant trauma, syphilis, operation or congenital nature. Perhaps of great importance was the fact that there seemed to be substance in the wall of the pulsating mass at every point accessible to the examining hand or finger.

Our attention was now given to the type of tumor. Tumors in this region are rare. They include chordomas, dermoids, ependymomas, teratomas,[5] Ewing's tumor, giant cell tumor, neuro- and fibro-sarcomata. Of this group of

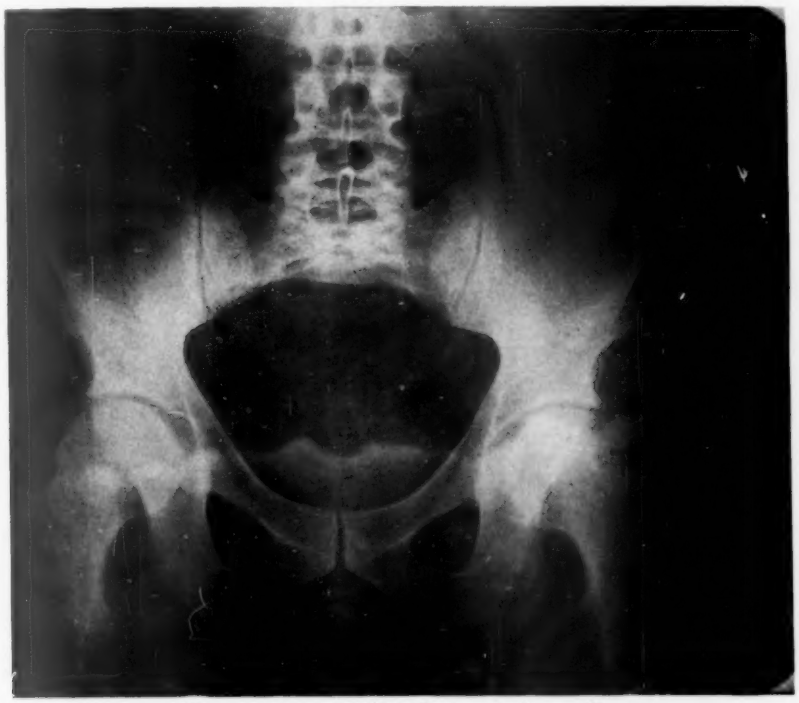

FIG. 1.—Preoperative X-ray of giant cell tumor.

possibilities, teratomas, dermoids, and neuro-fibromas usually arise from the ventral surface of the sacrum and seldom destroy that bone. Chordomas and ependymomas do not pulsate as a rule, and rarely is pulsation observed in a fibrosarcoma. Therefore, if neoplasm is the cause of the pulsating mass, it appears that the benign giant cell tumor or the malignant Ewing's tumor must be the responsible type. Rectal findings disclosed circumscription and slight mobility of the tumor, characteristics which suggested benignity. Aspiration biopsy was deemed inadvisable due to the pulsating nature of this tumor and possible subsequent intraneoplastic hemorrhage. However, it was accomplished and the tumor proven to be of the benign giant cell type.

The choice of a method for treatment was a serious matter. One fact seems to be clear in the minds of competent bone tumor students. Benign giant cell

tumors[3, 4, 6, 7, 8] can be treated either by radiation or surgery independently, but the combination of radiation therapy and surgery produces poor results. The advocates of both forms of therapy insist that if their method is chosen, it must be adequately and completely employed. Geschickter and Copeland[11] feel that "Surgery is the treatment of choice for giant cell tumors in general, and make no exception for pulsating giant cell tumors." Herendeen[6] is of the opinion that radiation successfully handles giant cell tumor in the majority of cases. Anticipating that this tumor may not be completely removed by surgical extirpation and realizing the attending dangers of surgical removal,

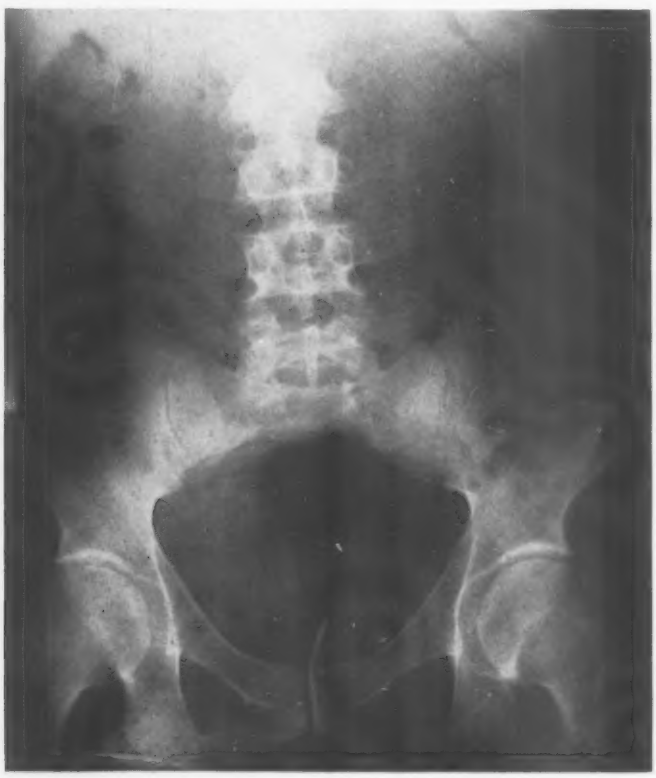

FIG. 2.—Postoperative X-ray of pelvis.

several radiotherapists were consulted in the matter. Each was hesitant, due to the pulsating nature of the neoplasm and fear that too much radiation would be necessary regardless of the division into numerous small doses, which would result in skin necrosis and probably alarming hemorrhage. Some questioned the ability of radiation to completely destroy the tumor and others felt that the resulting fibrosis of the skin and rectal wall would be deleterious, and one was concerned with the possibility of rectal fistulae. With these unenthusiastic remarks in favor of radiation in mind, we considered the surgical attack as the method from which the best result could be achieved. It meant sacrifice of

FIG. 4.—Anterior view of giant cell tumor.

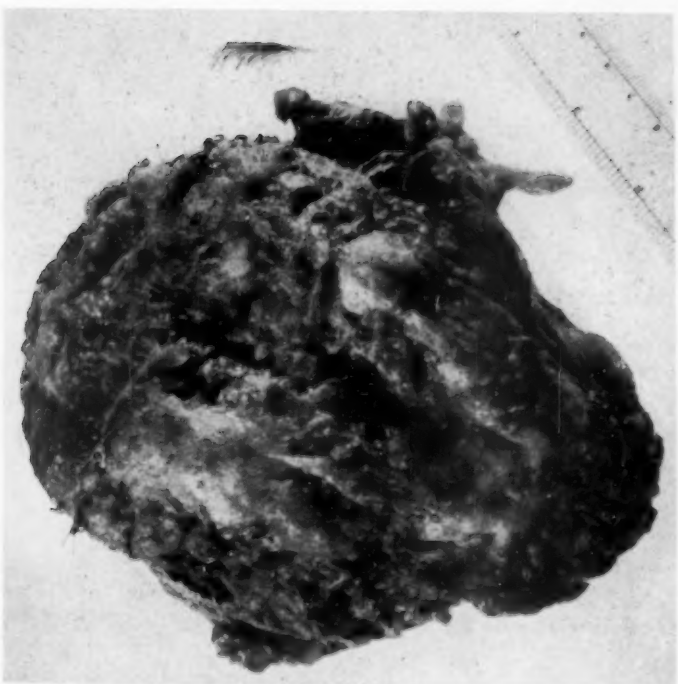

FIG. 3.—Posterior view of giant cell tumor.

sacral segments II, III, IV, V, the coccyx, and all the sacral nerves below S_I or S_{II}. We felt this not to be untenable even though it meant partial or complete paralysis of the bladder and rectal sphincters. But the ability of the surgeon to completely control hemorrhage and at the same time completely remove the tumor presented a hazardous problem.

Therefore, consideration for a surgical attack upon the tumor was at hand. The benignity of the tumor led us to postulate that if the tumor could be freed from its posterior attachments and the blood supply controlled, that it would be a relatively simple matter to establish a cleavage line and dissect

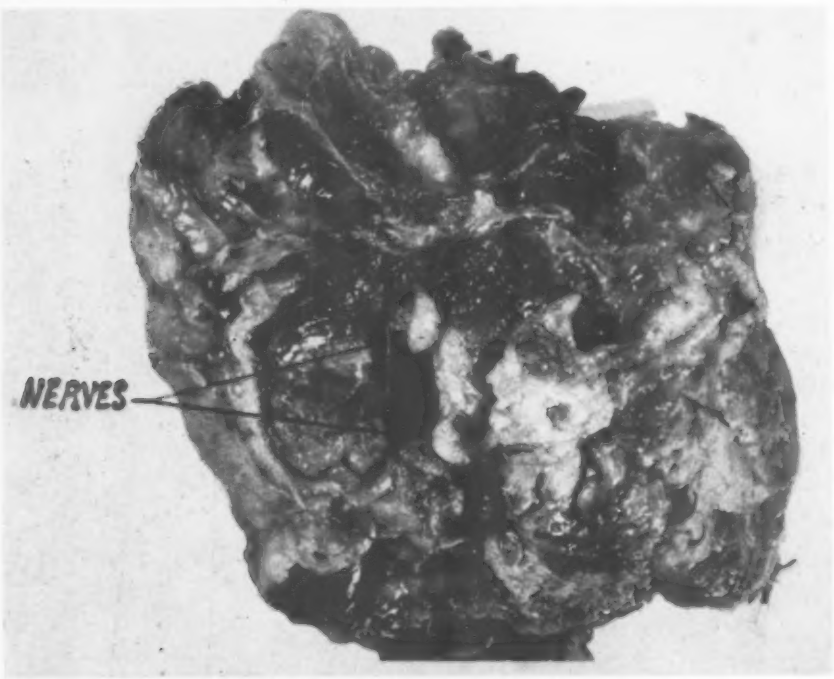

FIG. 5.—Superior surface of giant cell tumor.

it free of the rectum. If the tumor arose from the sacrum, the blood supply could be assumed to be dependent upon the middle or lateral sacral vessels and the hypogastric arteries. Hope for controlling these vessels posteriorly was vain.

Operations. On November 20, 1945, the first operation was done with the patient in the prone position. An elliptical incision was made in the skin at the projected lateral and longitudinal margins of the tumor. This was made slowly, because of profusion of subcutaneous blood vessels which were clamped and ligated with fine black silk. The lateral flaps were reflected with the same vascular difficulty. This exposed the fascia of the gluteus maximus muscle, the pre-sacral fascia and the pre-coccygeal fascia. The next excursion entailed the incision of these fasciae, encountering a greater number of blood vessels than in the subcutaneous tissue. When this was completed, the pulsating tumor arose from its bed and the pulsations were more pronounced. At the coccygeal end of

the mass, we were able to define a cleavage line for attempted dissection from the rectum, but the vascularity was so great that after 5 hours of total operating time, the procedure was abandoned and the skin closed with interrupted silk sutures. Two 500 cc. blood transfusions were given while the patient was in the operating room.

The patient recovered rapidly from this major attempt at posterior removal.

The location of the tumor was again considered in relation to its main blood supply which, we now correctly conjectured, must be in the hypogastric artery or one of its branches. Therefore, it was deemed wise to explore the tumor by laparotomy to determine the source and possibility of controlling the blood supply.

On December 4, 1945, a left rectus incision was made near the midline. When the peritoneal cavity was opened and small intestines displaced into the upper abdomen, the large tumor could be seen to be residing in the space behind the sigmoid, which

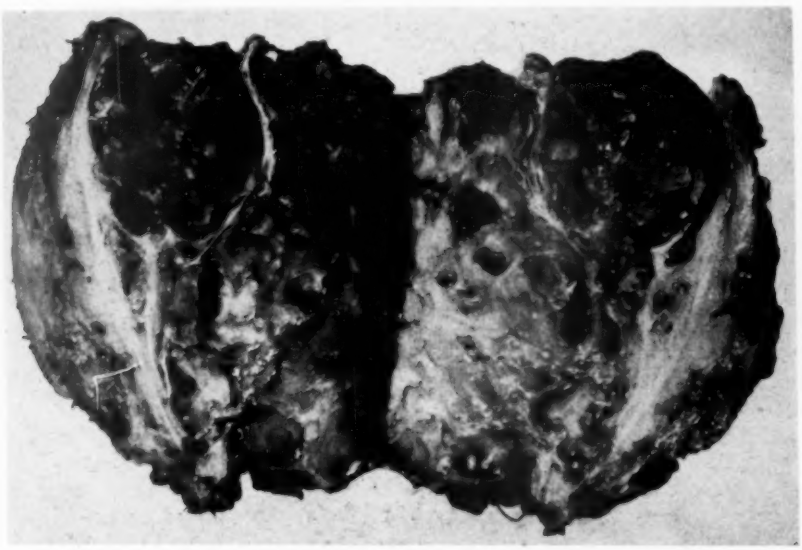

FIG. 6.—The sectioned giant cell tumor.

pushed this bowel anteriorly to the level of the anterior peritoneum. The common iliac vessels were exposed and when occluded, cessation of the pulsations in the tumor was observed. The hypogastric vessels were huge and could be seen entering the growth about one inch distal to their exit from the common iliac artery. Occlusion of these vessels also completely stopped the pulsation. The hypogastric vessels were now doubly ligated and transected. Although the pulsations had ceased, our experience posteriorly in the first operation had commanded great respect for the vascularity of this tumor, and to prevent any chance of collateral supply from the arteries below the hypogastric, both common iliac arteries were occluded with umbilical tapes. The laparotomy wound was closed with through and through silver wire sutures and the patient was placed in the prone position. The old posterior wound was now reopened and the cleavage plane at the coccygeal end reestablished. With great ease and little bleeding, we were able to incise the gluteus maximus muscle and then by dissecting under the tumor, freed the tumor from the rectum, sigmoid, and a few lateral muscular attachments. Now the tumor was attached only to the inferior border of the first sacral vertebra. By chiselling across the substance of good bone, the removal was completed. The tumor was torn in one area during the chiselling process. The bone was finally debrided of its neoplastic invasion by rongeuring. Very little bleeding accompanied this removal.

The rectal wall was not injured. The skin was closed loosely with drainage of the huge dead space. During the dissection an attempt was made to save as many of the sacral nerves as possible. The first sacral nerves were intact, but the remainder were necessarily sacrificed.

The patient was again placed in position for laparotomy, the wires removed, exposure regained, and the tapes removed from both common iliac vessels. The tapes had been left in place for 2 hours and 45 minutes. The abdominal wall was closed in layers with

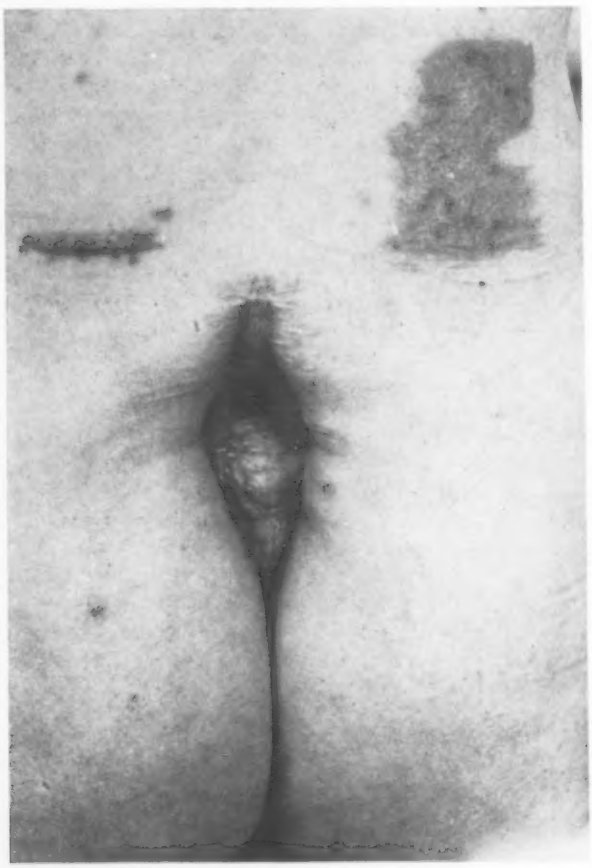

FIG. 7.—Healed posterior wound.

silk, and the patient returned to the ward in good condition. Dorsalis pedis and posterior tibial arteries were pulsating after the tapes were removed, and have functioned properly ever since.

Microscopic section showed this to be an extremely vascular but typical benign giant cell tumor with areas of bony tissue scattered throughout its substance.

Course. A retention catheter was placed immediately following the operation. An examination of the rectal sphincter revealed a total lack of sphincter tone. From the interruption of the pre-sacral nerve and lower sacral nerves, urinary and rectal incontinence were expected. The patient experienced a smooth postoperative course. The laparotomy wound healed per primam, but the sacral wound separated, the dead space granulated to the skin level, and this area was finally healed by Thiersch grafting in

April, 1946. The patient was ambulatory on the 12th postoperative day and remained ambulatory except for a short time following the grafting operation. Paralysis of the urinary sphincter persisted and is handled by the regimen instituted by the use of a Cunningham clamp. The rectal sphincter, although paralyzed, has not been the cause of great discomfort. A daily bowel movement in the early morning was the established habit, and soiling takes place only when infrequent diarrhea appears.

The patient's general condition began to improve and during the course of four months, he had regained weight to the normal amount, became strong, and appeared in the best of health. He went home on furlough for long periods of time. About 9 months after the operation, he was rehospitalized with a minimal chest lesion, thought to be tuberculosis. It was considered as a matter of safety to regard the infection as tuberculous, in spite of negative sputa and gastric washings. He was treated for this chest lesion for a period of 6 months. At this time the pulmonary lesion had completely disappeared. His weight was normal and the status of the urinary and rectal sphincters was unchanged. The presence of the tumor, with its attending malnutrition, and the rigors of the operation may have been factors contributing to the onset of the tuberculous infection.

Follow-Up. The patient has been able to walk without great difficulty although he complains of weakness in the legs and numbness along the back of the thighs and legs. Upon discharge in the fall of 1946, the rectal and urinary sphincters were not functioning, there was anesthesia over a small area perianally and hypesthesia extending down the posterior aspects of both legs and in the heels. In response to a questionnaire, the patient sent a reply indicating the following status on March 4, 1948, approximately 2 years and 3 months following the radical removal of the tumor. He performs light work around a small shop and his house, and claims that the legs "play out" after vigorous exercise. There is no control of urinary or rectal sphincters. Cunningham clamp is worn, constipating diet is followed. These handicaps are not as distressing as the leg weakness, according to the patient. His weight is normal, appetite good. Roentgenograms of the chest and sacral region were done in December, 1947, which reveal maintenance of the disappearance of the pulmonary lesion and non-recurrence of the tumor. It appears reasonable to expect permanent cure of this benign tumor, now that there is no clinical or roentgenological evidence of recurrence after the passage of 2 years and 3 months postoperatively.

SUMMARY

1. Resection of the coccyx and sacral vertebrae II, III, IV and V has been accomplished in a patient with a large pulsating benign giant cell tumor originating in the sacrum.

2. The method employed is described. It entailed laparotomy, ligation of the hypogastric arteries and temporary occlusion of the common iliac arteries before successful posterior resection could be done.

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CHOLEDOCHUS CYST ASSOCIATED WITH CONGENITAL ATRESIA OF THE BILE DUCTS*

(REPORT OF A CASE)

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CHOLEDOCHUS CYST is a rare anomaly of the biliary tract, approximately 180 authentic cases having been reported to date. The literature has been thoroughly reviewed in recent years by Smith,[7] Shallow, Eger and Waggoner[6] and McLaughlin.[4]

Many authors have advanced theories to explain the etiology of this condition. The simplest and most widely accepted is that of Yotuyanagi[9] who considers these cysts to be congenital anomalies due to maldevelopment of the biliary tube in the eighth week of fetal life. At this stage the common duct recanalizes from a solid cord of epithelial cells, and abnormalities may lead to atresia or cystic areas. Such a theory places the etiology of this condition on the same basis as that suggested by Bremer[1] for duplication of the bowel. In the latter condition areas of atresia and cysts are sometimes present in the same intestine.[5]

It is rather surprising that co-existing choledochus cyst and bile duct atresia has not been reported previously, but a search of the literature fails to reveal such a case. In several instances obliteration of the common bile duct below the cyst has been present. In none of these was there any reason to believe the obstruction a congenital atresia since in all cases there was a prolonged period during which the patient was free from jaundice. Shallow, Eger and Waggoner[6] consider these to be cases of congenital stenosis with subsequent inflammatory obliteration of the duct.

The following case is believed to be unique in that a cyst of the common bile duct was associated with congenital atresia of both hepatic and common bile ducts.

CASE REPORT

L. J., a female infant age 4 months, was admitted to the Royal Victoria Hospital April 14, 1948. The mother stated that the child had been jaundiced since birth and that she had passed white stools from the first bowel movement. There had been some variation in the intensity of the jaundice from day to day.

On admission the child was afebrile. There was moderate icterus of the skin and sclerae but the baby was in good condition and well nourished. Physical examination showed the liver to be moderately enlarged, but no other abdominal masses could be

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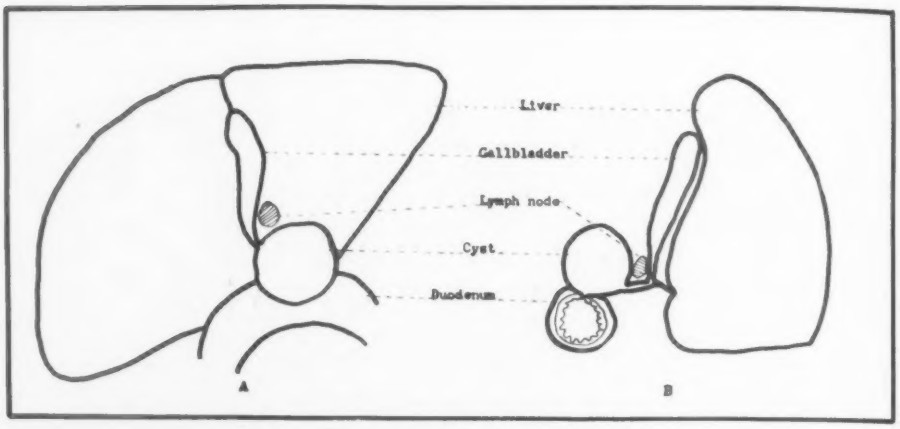


FIG. 1.—Diagram of findings at operation.

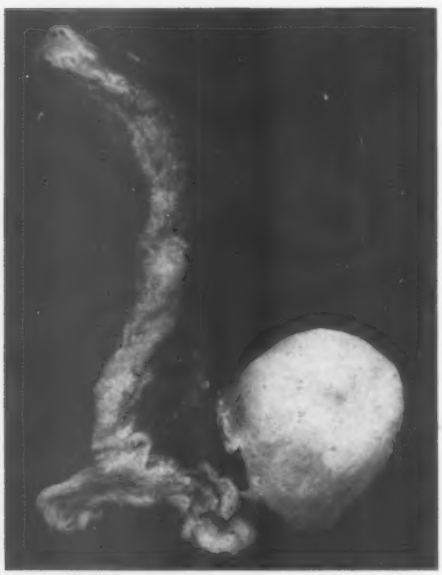


FIG. 2.—Photograph of specimen.

palpated. Laboratory investigation revealed the following data:

1. Father, mother and child were all blood group O, Rh positive.

2. Blood Wassermann negative.

3. The urine consistently contained bile and the faeces showed traces of urobilinogen and bilirubin.

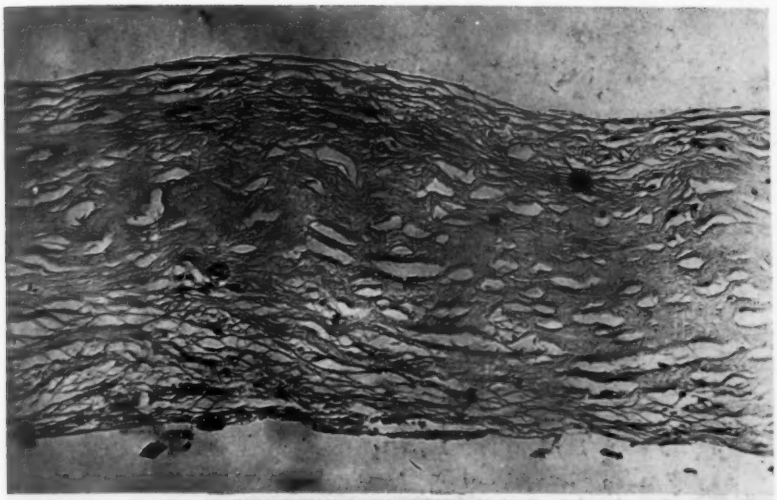
4. Blood chemistry—

NPN	24.7	mg.%
Total protein	5.71	Gm.%
Albumen	4.1	Gm.%
Globulin	1.61	Gm.%
Alkaline phosphaton	50.4	units
Bilirubin—Direct	5.7	
Indirect	7.6	
D/I	75%	
Cephalin cholesterol	Negative	
Thymol turbidity	1.4	
Thymol flocculation	Negative	

5. Haemogram normal. Prothrombin time 20 sec. (100% of normal).

These findings were interpreted as indicating an extrahepatic obstructive jaundice and the differential diagnoses considered were, congenital atresia of the bile ducts, obstruction of the common duct due to inspissated mucus, and choledochus cyst. Laparotomy was performed May 1, 1948, under intratracheal ether anesthesia (Fig. 1). On opening the abdomen the liver presented into the wound. It was markedly enlarged and green in colour. A gallbladder was present, and aspiration of it yielded colorless mucus and no bile. The peritoneum overlying the common duct was divided and a cyst-like swelling 2 cm. in diameter was seen replacing the lower end of the duct. Aspiration of this again showed mucus but no bile. Saline was injected into the gallbladder and this caused filling of the cyst. Further dissection revealed a normal cystic duct communicating with the common bile duct just above the cyst but the common hepatic duct was represented by a fibrous cord with no lumen (Fig. 2). The cyst was removed to obtain better exposure and in doing so the duodenum was inadvertently opened, making it impossible

FIG. 3



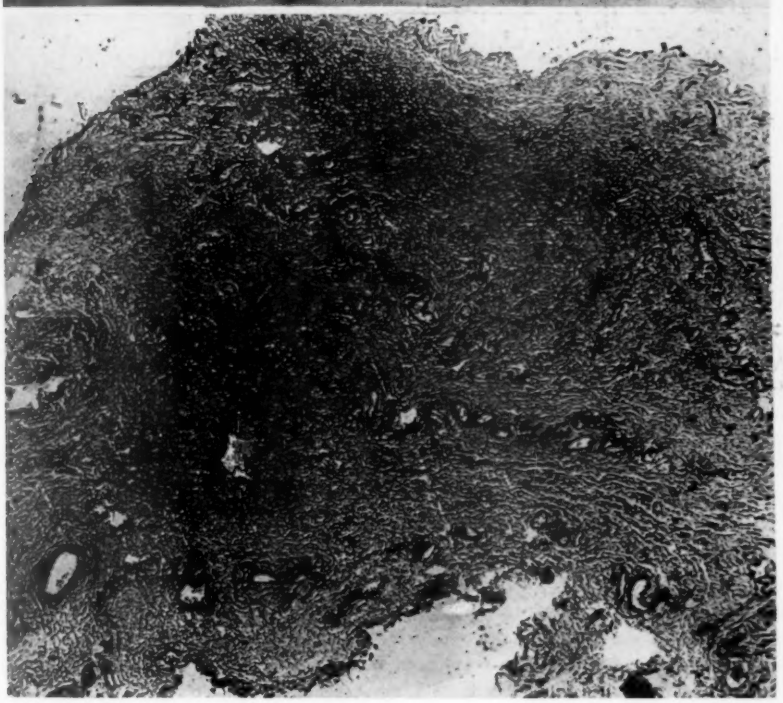


FIG. 4

FIG. 3.—Section through cyst wall showing laminated fibrous tissue and no epithelium.

FIG. 4.—Section through common bile duct with no evidence of lumen.

to demonstrate whether or not a communication had previously existed between it and the cyst. An attempt was made to obtain bile by aspiration of the atretic hepatic ducts but this was unsuccessful. The condition was considered to be inoperable. The cyst and gallbladder were removed and the abdomen was closed. The postoperative course was complicated by peritonitis, and the child died two weeks after laparotomy. Autopsy revealed that the intra-hepatic bile ducts were not completely atretic, but their walls were thickened and their lumens very small in diameter (Fig. 5).

Pathologic Report. (Dr. T. R. Waugh). The specimen consists of a gallbladder

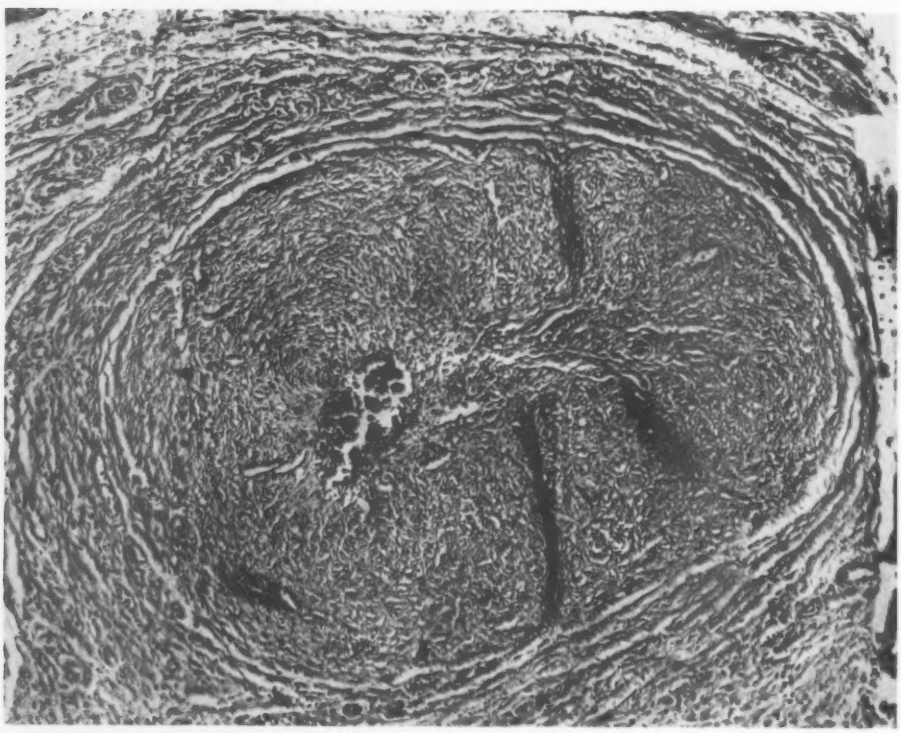


FIG. 5.—Section through the common hepatic duct. The lumen is small and contains bile. The wall is thickened and hypertrophied.

5 cm. in length terminating in a narrow cystic duct which passes into a short segment of common duct 1.8 cm. in length. The serosal surface is pearly gray, smooth and glistening and covered with a few fibrous tags. The lumen of the gallbladder is patent and empty. Both hepatic and common ducts are without lumens consisting of flattened tough fibrous tissue.

There is also a detached roughly spherical unilocular cyst 1.8 cm. in diameter. The wall is thin, white, smooth and fibrous.

Microscopic examination of the gallbladder shows the mucosa intact. Numerous Rokitansky-Aschoff sinuses are present and the muscularis is thick with occasional foci of lymphocytes in the lamina propria.

Sections of the cyst show it to consist of dense fibrous connective tissue arranged as parallel collagenous strands (Fig. 3). The inner surface lacks an epithelial lining.

Sections from the distal portion of the specimen reveal no evidence of a lumen in either the hepatic or common bile ducts (Fig. 4).

Diagnosis. Simple cyst—common bile duct.
Atresia of hepatic and common bile ducts.

SUMMARY

1. A case of choledochus cyst associated with congenital atresia of the bile ducts is reported.

This is believed to be the first time that such a finding has been recorded in the literature.

2. The coincidence indicates that the etiology of both conditions may be due to abnormalities in the development of the bile ducts during recanalization of the solid stage which occurs in the 8th week of fetal life.

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TRAUMATIC RUPTURE OF THE CHOLEDOCHUS, ASSOCIATED WITH AN ACUTE HEMORRHAGIC PANCREATITIS AND A BILE PERITONITIS*

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Traumatic rupture of the common bile duct occurs very infrequently and is usually fatal because of concomittant injuries to the liver, pancreas, spleen and the intestinal tract. Invariably liberation of the bile into the peritoneal cavity results in a biliary peritonitis, with its attendant distention, toxicity, and malnutrition. The accumulated biliary ascites increases the intra-abdominal pressure, elevates the diaphragm, and inhibits the use of the abdominal muscles, so that the process of respiration is very inadequate and thereby conducive to a serious state of generalized anoxia. These altered physiologic conditions portend an unfavorable prognosis unless they can be corrected by surgical intervention.

ETIOLOGY

Traumatic rupture of the extrahepatic biliary system is usually produced by direct force. It may be of a penetrative nature as incurred in gun shot wounds, or compressive as encountered in crushing injuries. Violent compression of the anterior abdominal wall against the lumbar vertebrae may lacerate or cause an avulsion of the common bile duct.

Case History.—H. G., a white boy, 7 years of age, entered the Latter Day Saints Hospital on May 6, 1947, because of an intense jaundice associated with distention, persistent vomiting, dehydration, and anoxia. The week before he had received a compressive injury to his abdomen, when a tractor crushed him against a manure spreader. The "hitch" on the tractor had struck him above and to the right of the umbilicus, forcing the impinged viscera against the vertebrae.

He was taken to a local hospital where he was treated for mild shock and then dismissed. Four days later he was readmitted to this hospital because of an intense paraumbilical pain which radiated to the right shoulder. Nausea, vomiting, dehydration and jaundice progressively increased during the next 72 hours, his condition became so serious that he was transferred to the Latter Day Saints Hospital.

The boy's acute illness was evidenced by a temperature of 104.8 F., a respiratory rate of 62, and a pulse rate of 186. His abdomen was so distended that breathing was most laborious and superficial. A bilateral pleural effusion, abdominal ascites, jaundice, and an intense acidosis added to the gravity of his condition.

Emergency treatment consisted of oxygen therapy, gastric decompression, and the intravenous administration of electrolytes, protein hydrolysates, whole blood, and blood plasma. Continuous penicillin therapy was instituted. An abdominal paracentesis recovered 3,000 cc. of a clear golden-colored bile, cultures of which were negative for bacterial

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contamination. Laboratory studies resulted in the following data: 2,800,000 RBC, 64 per cent hemoglobin, 18,200 WBC, with a differential polymorphonuclear count of 88 per cent. The icteric index was 76. The urine contained 4 plus bile, 3 plus acetone bodies, and 2 plus albumin. The stools were acholic. The prothrombin time was 46 seconds. The total plasma proteins were 4.8 Gm.; serum globulin 1.8 Gm.; serum albumin 3 Gm.

After 4 days of intensive preoperative preparation the abdomen was opened under a balanced anesthesia consisting of cyclopropane and curare. Twenty-three hundred cubic

FIG. 1.—A drawing showing conditions found at the time of operation. The traumatic laceration of the posteromedial wall of the choledochus was situated so the bile could drain into the lesser omental sac. Note the multiple lacerations of the pancreas.

centimeters of normal-appearing bile was aspirated from the abdominal cavity. The stomach and colon were elevated and pushed forward by a large fluctuating mass. The tumefaction proved to be 2100 cc. of bile, which had become loculated within the lesser omental cavity. There was no gross evidence of injury to the liver and both the gallbladder and cystic duct were collapsed, but otherwise normal.

How had the bile gained access to the peritoneal cavity? In order to answer this question 50 cc. of a solution of 70 per cent diodrast was injected into the collapsed gallbladder, and a visualizing cholangiogram was taken. The gallbladder, cystic duct, common

hepatic duct, and the upper segment of the choledochus were clearly visualized. None of the contrast medium was able to pass through the ampulla of Vater, indicating that the edematous pancreas had produced a compressive occlusion of the ampullary orifice. In the upper third of the choledochus a small stream of diodrast was seen to penetrate the ductal wall and escape into the lesser omental cavity. The extravasated diodrast localized the laceration as being on the posteromedial wall of the common bile duct. (Fig. 1).

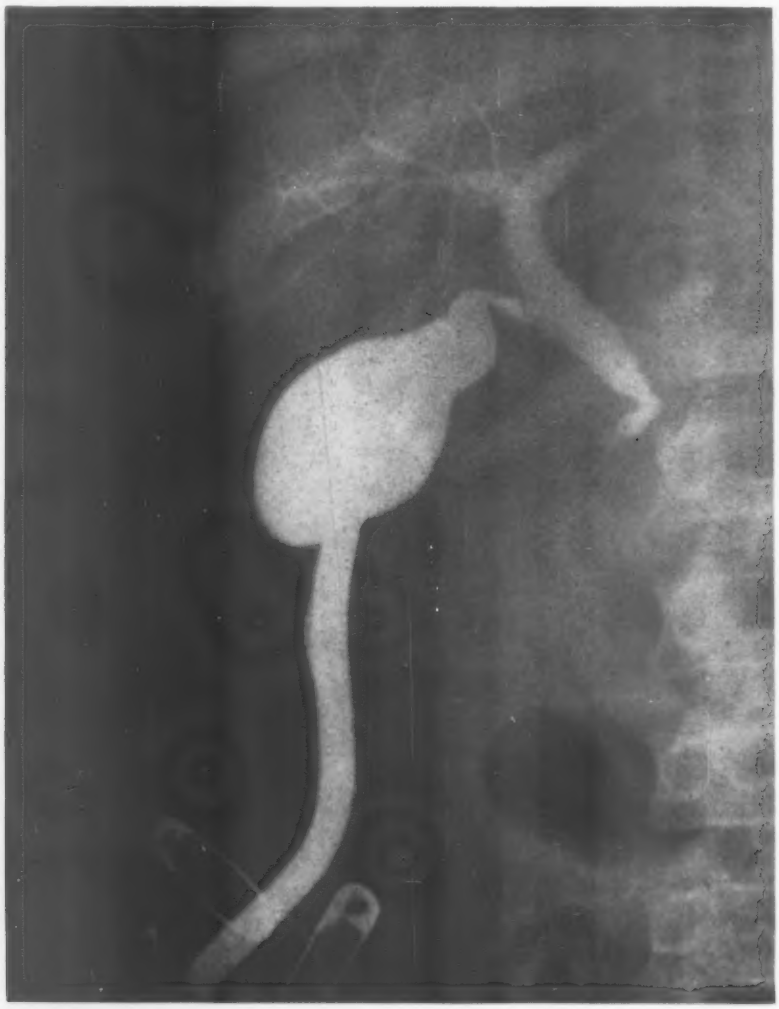

FIG. 2.—A postoperative cholangiogram obtained by injecting 54 cc. of solution of 70 per cent diodrast into the cholecystostomy tube. Note that gallbladder, cystic duct, common hepatic duct, and proximal portion of the choledochus are well visualized. The contrast medium, however, was unable to pass through the ampulla of Vater because of concentric compression of the edematous and traumatized pancreas.

These operative cholangiograms presented several important findings: (1) The laceration was situated on the posteromedial wall of the common bile duct so that the bile escaped into the lesser omental cavity; (2) a traumatic pancreatitis had further com-

plicated the problem by effecting a complete occlusion of the ampulla of Vater; and (3) the gallbladder and cystic duct were both patent and could be used to decompress the common hepatic bile duct while the obstructive pancreatitis was subsiding. A decompressive cholecystostomy was accomplished by inserting a large rubber catheter into the gallbladder and bringing it out through a stab wound. A large Penrose drain was placed in the foramen of Winslow so as to drain the bile from the lesser omental bursa. No attempt was made to suture the traumatized choledochus.

FIG. 3.—A postoperative cholangiogram made several days later. Observe that the contrast medium now flows into the duodenum, and that the gallbladder, cystic duct, and choledochus are no longer dilated. The pancreatitis has not completely subsided for the "thread like pattern" indicates a narrowing of the ampullary segment of the common bile duct.

Supportive therapy consisted of the administration of whole blood, blood plasma, protein hydrolysates, vitamins and electrolytes in sufficient quantities to maintain a positive balance. On the fifth postoperative day an additional 1,500 cc. of bile was removed from the peritoneal cavity by an abdominal paracentesis, in spite of the fact that there had been a copious flow of bile from the cholecystostomy tube. A postoperative

cholangiogram was obtained by introducing 54 cc. of diodrast into the gallbladder, through the cholecystostomy tube. The entire extrahepatic biliary system was clearly visualized. Apparently the rent of the common bile duct had completely healed for none of the diodrast escaped into the lesser omental cavity. The ampulla of Vater, nevertheless, was still obstructed, indicating the necessity for continued decompression. (Fig. 2)

One week later, another series of cholangiograms were made and they demonstrated a complete functional recovery of the choledochus. The laceration had been repaired and the obstructive pancreatitis had subsided sufficiently to permit the diodrast to pass down the common bile duct into the duodenum (Fig. 3). There was no further need for decompression of the common bile duct hence the drainage tube was removed. Ten months have elapsed since the injury and his recovery has been most pleasing as evidenced by a gain of 15 pounds in weight.

DISCUSSION

Spontaneous or traumatic rupture of the extrahepatic biliary system invariably results in a troublesome bile peritonitis. The bile salts and acids evoke a mild inflammatory irritation of the peritoneum and omentum, but unless there is a concomittant bacterial infection the inflammatory reactions are minimal. It was interesting to note that 8,900 cc. of bile was removed from this youngster's peritoneal cavity but no inflammatory exudate was encountered at the primary operation. The appearance of jaundice usually coincides with the onset of toxic symptoms. According to Harkins, Harmon and Judkins,[2] a secondary bacterial infection can and does enhance the toxicity of the biliary peritonitis.

This case demonstrates the fact that lacerations of the choledochal wall will heal spontaneously if the intraductal pressure can be maintained at a low level by continuous decompression. This is verified by the rapidity with which the choledochus heals after drainage tubes are removed. It is imperative, however, that the external decompression be maintained until there has been a complete reparation of the ductal wall, and until the patency of the ampulla of Vater had been confirmed.[3] Such information can be obtained by serial cholangiographic studies.

It is a common belief that if pancreatic ferments are activated by bile salts, autodigestion of surrounding tissues occurs. It is significant, however, that this patient had multiple lacerations of the pancreas, which were severe enough to produce hemorrhagic changes within the pancreas itself, yet there were no signs of tissue digestion around the pancreas, in spite of the presence of extravasated bile. Careful examination failed to show any evidence of saponification of adipose tissues. Apparently this fermentative autolysis occurs only when dead or devitalized tissues are present, as normal tissues are able to withstand the digestive actions of these combined ferments. This supposition agrees with the observations of Dragstedt, Haymond, and Ellis.[1]

SUMMARY

1. Traumatic rupture of the common bile duct may be produced by injuries that are either penetrating or compressive in nature.

2. A bile peritonitis results from the extravasation of bile into the peri-

toneal cavity. A total of 8,900 cc. of bile was aspirated from the abdominal cavity of a seven-year-old boy, as described in this paper.

3. Lacerations or rents of the extrahepatic biliary system can be quickly and accurately localized by means of operative cholangiograms. These "radiographic blueprints" provide the surgeon with an accurate visual pattern of the reconstructive problem which confronts him.

4. A case is presented wherein a traumatic rupture of the posteromedial wall of the common bile duct occurred, permitting the extravasation of bile into the lesser and greater peritoneal cavities. The bile peritonitis was aggravated by a concomittant acute pancreatitis which completely occluded the ampulla of Vater, thereby compelling all the bile to escape through the lacerative opening.

5. This case demonstrates that lacerations of the choledochal wall will heal spontaneously providing the extrahepatic ductal system is kept decompressed by external drainage. The decompressive tubes should be left in situ until serial cholangiograms demonstrate that the ductal defect has been completely healed and that the associated pancreatitis has subsided sufficiently to permit the free passage of bile through the ampulla of Vater into the duodenum.

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MULTIPLE CARCINOMAS OF THE STOMACH*

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WHILE MULTIPLE MALIGNANCIES of the gastro-intestinal tract are second in frequency to skin lesions,[1] multiple malignant neoplasms of the stomach are comparatively rare. Warren and Gates,[1] in 1932, in a review of the literature, reported 25 primary multiple stomach malignancies. Brindley, Dockerty and Gray[2] reported 23 multiple malignancies of the stomach among 1,184 carcinomas of the stomach seen at the Mayo Clinic between 1932 and 1941, and they add an additional one with four carcinomas of the stomach. Hellendall[3] and Rickles[4] each reported one case, the latter having one with 5 individual carcinomas.

Perhaps heredity, congenital anomalies or hormonal influences play a role in multiple carcinomas.[3] Rhoads[5] states that studies in recent years provide evidence that cancer may be a local manifestation of a general disease. This may explain in part the frequency of primary multiple tumors.

Warren and Gates[1] noted that multiple cancers occur at approximately the same age as single ones and that they occur more frequently than can be explained on chance alone. They make use of the following criteria in evaluating multiplicity:

1. Each of the tumors must present a definite picture of malignancy.
2. Each must be distinct and the probability of one being a metastasis of the other eliminated.

They also feel that as long as the tumors are clearly independent, their location relative to one another is immaterial. In their series of 1,078 cancer autopsies, the frequency of primary multiple tumors was 3.7 per cent, whereas on the basis of all statistics, the frequency is 1.84 per cent of cancer cases. (The question of immunity or a predisposition to multiple tumors is still debatable.)

The occurrence of three cases with primary multiple carcinomas of the stomach from 1943-1947 in one institution is rare indeed, and hence we are presenting these cases.

CASE REPORTS

Case 1.—H. M., a 46-year-old white male, was seen May 19, 1947, and stated that he had been treated for about 15 years for anemia. About one year ago, began having pain in the left upper quadrant; 7 months history of loss of appetite; 10 days ago had a vomiting spell with coffee ground material present. Weight loss 30 lbs.

* Submitted for publication June, 1948.

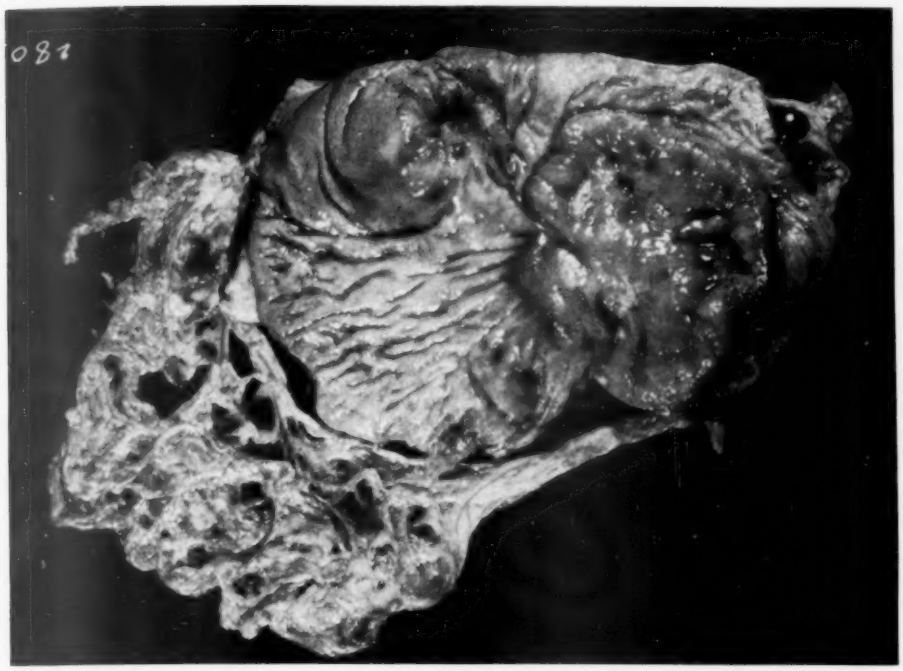

FIG. 1.—Two lesions measuring 9 cm. and 4 cm. invading muscle.

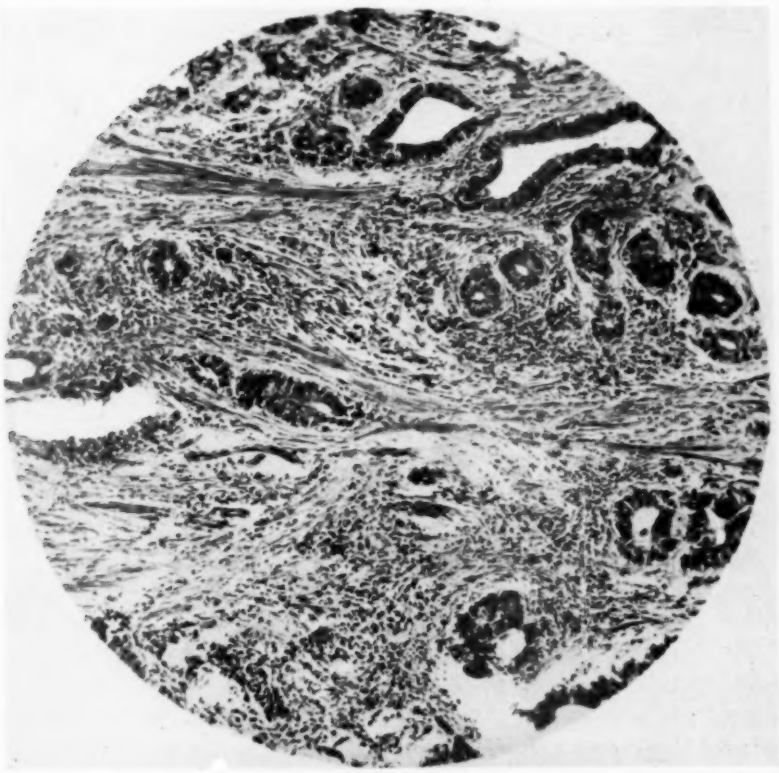

FIG. 2.—Adenocarcinoma invading the musculature.

Had roentgenograms elsewhere, June 1946, which were apparently negative. Had repeat roentgenograms, January 1947, when a large, ulcerating lesion was noted in the pre-pyloric region of the stomach with surrounding filling defect and fixation. Diagnosis of a massive, ulcerating carcinoma with obstruction was made. Gastro-intestinal series done here on admission showed a spastic esophagus in the lower end with some hesitation, but with no definite evidence of tumefaction. The 24-hour films showed 60 per cent residue in the stomach. Films also confirmed impression of previous films, namely, that a gastric carcinoma was present.

Physical examination. A pale-looking, thin male in no acute distress. No tumefactions noted anywhere. Abdominal examination negative. No Blummer's shelf. Wassermann negative.

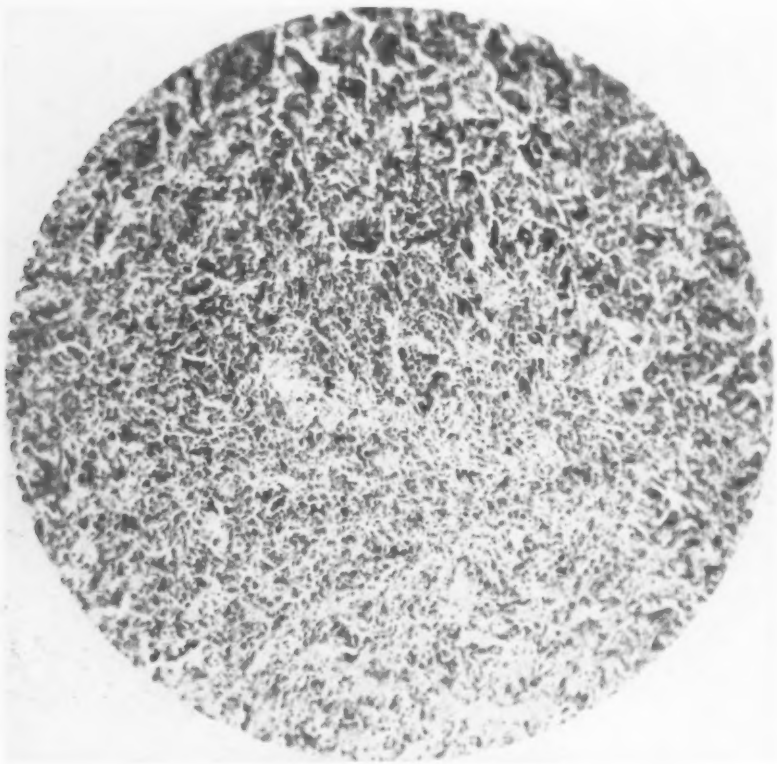

FIG. 3.—Anaplastic carcinoma with diffuse infiltration.

Laboratory data:

Hemoglobin: 65 per cent (9.08 Gm.)
RBC: 3,140,000
WBC: 9,250
Alb.: 3.66; globulin: 2.58
NPN, sugar and chlorides within normal limits.

Patient was placed on our usual high caloric, high protein, high vitamin diet and prepared for two weeks with blood transfusions and diet until his hemoglobin was 75 per cent; red blood count 3,800,000; hematocrit 47 per cent; and he had gained weight.

The plasma proteins did not rise. In view of the low blood volumes in patients with gastro-intestinal cancer and the persistent hypoproteinemia in spite of increased caloric and protein intake, our main concern was to treat the anemia preoperatively. We felt that the two-week nutritional preparation and the hemoglobin of 75 per cent was sufficient to allow us to operate with safety.

The patient was operated on and multiple carcinomas of the stomach were found. One involved the cardia and the other, the pre-pyloric region.

Gross. Stomach specimen shows a cardiac lesion 9 cm. in diameter. (1) The center of the growth showed ulceration with irregular, raised proliferation in the periphery. The tumor was fairly firm and invaded the muscular coat. About 2½ cm. from this growth, another tumor measuring 4 cm. in diameter (2) was found that invaded the muscular wall.

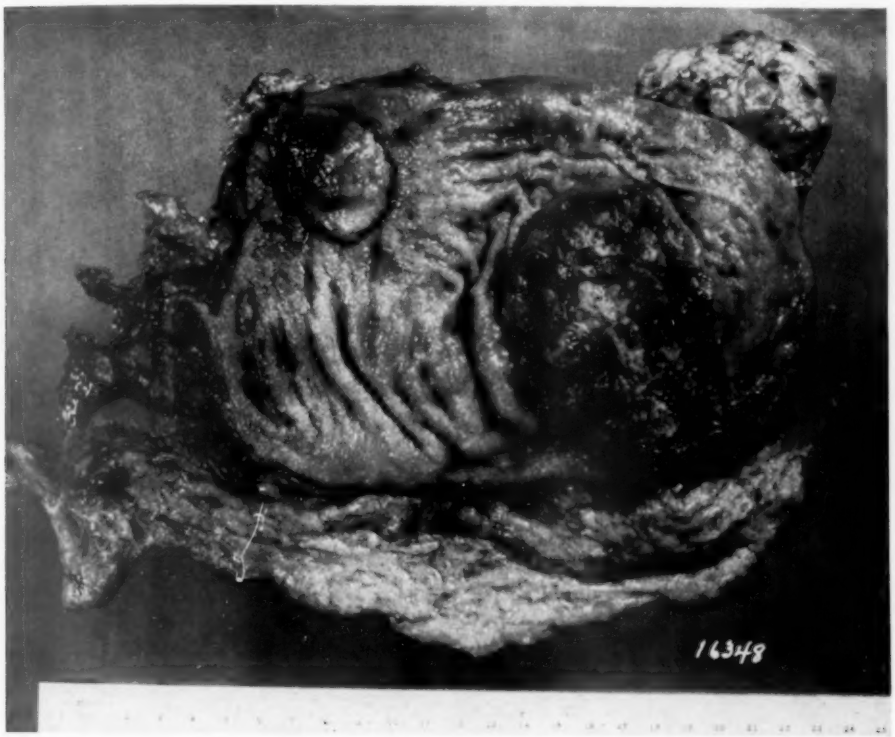

FIG. 4.—Two lesions measuring 9 cm. and 3 cm. infiltrating the musculature.

Microscopic: (1) Sections show an adenocarcinoma invading the musculature of the stomach. Gland formation is prominent.

(2) Sections show a diffuse infiltration of the stomach by a carcinoma. The growth is anaplastic in character and does not show gland formation.

Operation: A total gastrectomy was done via the abdominal route. Patient received 1000 cc. of blood in the operating room.

Postoperative Course: Uneventful. Patient was discharged in 14 days. At no time did he experience symptoms suggestive of the dumping syndrome. He is now, June, 1948, on a bland diet routine taken in 5 feedings. He is gaining weight and working.

Case 2.—T. N. Patient was seen here September, 1945, with a history of abdominal

pain for 8 months, loss of appetite for one week, loss of 28 lbs. in a year, weakness 4 to 5 months. Patient stated that for the past 5 months he has had constant epigastric pain, occasionally relieved by the ingestion of food. He also stated that he was treated in 1943 for a gastric ulcer, but at no time did he have roentgen-ray studies.

Physical examination revealed a 64-year-old white male in no acute distress. Abdominal examination: Liver, spleen, and kidneys not palpable. There was definite tenderness in the epigastric region, but no tumefactions were noted. Rectal examination was essentially negative.

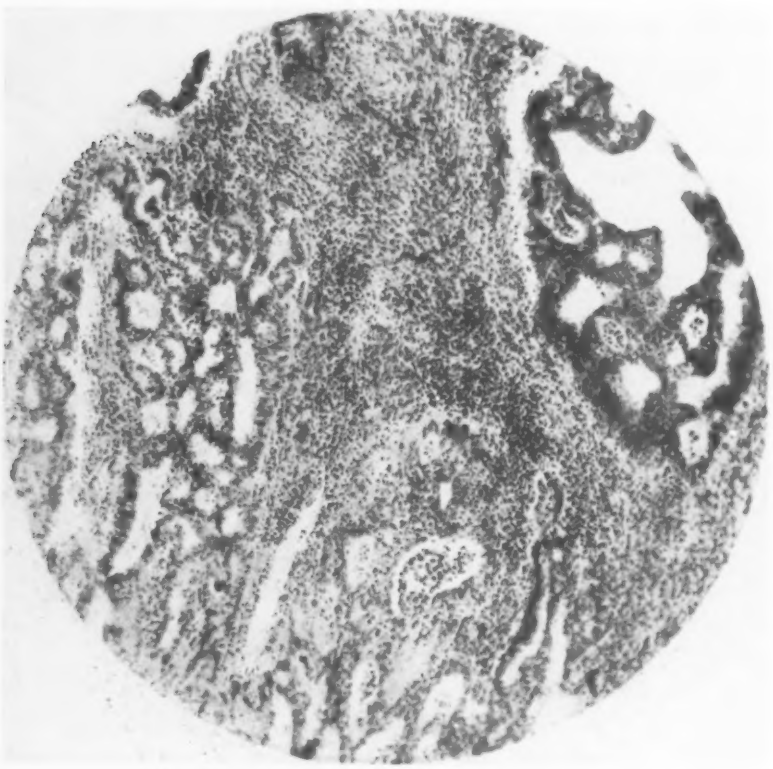

FIG. 5.—Infiltrating adenocarcinoma.

Roentgenograms: Fluoroscopic examination revealed a normal esophagus. The stomach was slightly large, modified fish-hook in type and low in position. Fluoroscopy and roentgen-ray films revealed a constant filling defect on the lesser curvature of the body of the stomach near the cardia. Peristalsis was normal; emptying began immediately and the cap was normal. The 3-hour film showed the stomach to be empty. Impression was that of an advanced carcinoma of the stomach.

Gastroscopic examination: The antrum and angulus were seen and showed no evidence of pathology. Peristalsis was very active. On the lesser curvature, in the body of the stomach, could be seen a large, ulcerating lesion, the edges of which were raised. The picture was typical of carcinoma of the stomach.

Patient was admitted to the hospital November 2, 1945, for a gastric resection.

Laboratory data:

Hemoglobin: 96% (13.8 Gms.)
RBC: 5,080,000
WBC: 9,450
Hematocrit 45%
Gastric analysis was negative for HCl in all samples with faint trace of blood.
Blood sugar 107 mg.%, NPN 43, Chlorides 435.

Patient was prepared in the usual manner with transfusions and diet and on November 11, 1945, a subtotal gastric resection was done. Two distinct areas of malignant degeneration were noted; one in the body of the stomach near the cardia and the other in the

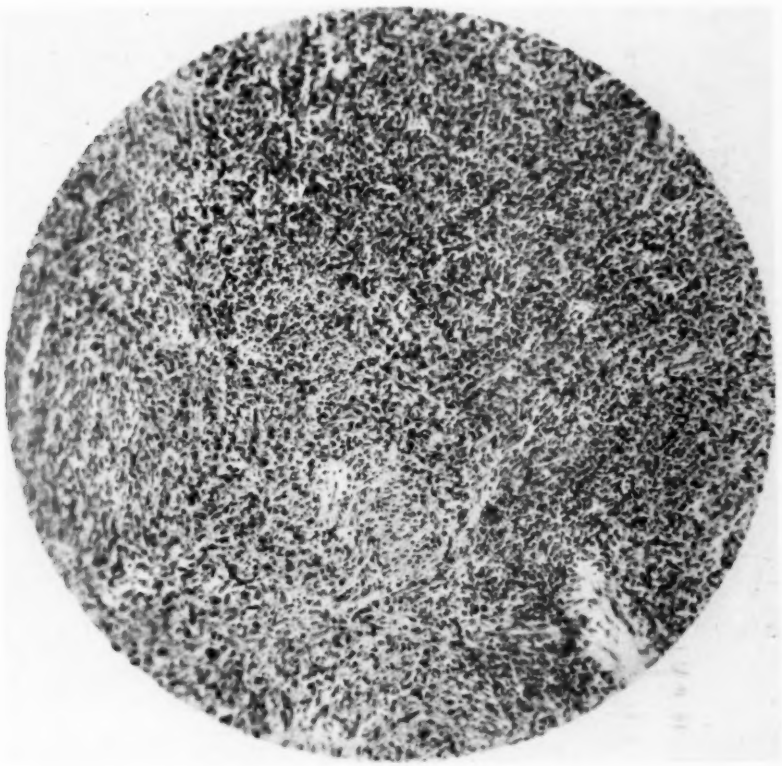

FIG. 6.—Anaplastic infiltrative carcinoma.

antrum. Regional malignant lymphatic spread was noted along the course of the left and right gastric arteries necessitating almost complete resection of the stomach.

Gross. Specimen from the stomach showed two distinct tumors. The larger one at the cardiac end measured 9 cms. in diameter. (3) There was central ulceration with irregular papillary proliferations in the periphery. The tumor was soft in consistency and reddish in coloration. The second lesion measured about 3 cms. in diameter. (4) It was papillary in type and reddish in coloration. Both tumors were found to infiltrate the gastric musculature.

Microscopic. (3) Sections show an infiltrating adenocarcinoma. (4) Sections show an anaplastic infiltrative carcinoma.

Patient's postoperative course was uneventful and he was discharged November 21st. Has been seen at 3-month intervals since then and a gastrointestinal series done March 25th revealed no evidence of recurrence. Patient was last seen September, 1946, at which time he complained of symptoms typical of the dumping syndrome. There was no intra-abdominal evidence of recurrent tumefaction. No evidence of obstruction. Rectal examination was also negative. A questionnaire reply, May, 1948, stated that patient had died of bronchopneumonia.

Case 3.—J. R. K. Patient was a 64-year-old white female, admitted in January, 1943. She was a gravida 2 and had her menopause at 46. Had a bloody vaginal discharge one

FIG. 7.—Two lesions measuring 10 x 6 cm. and 4 x 6 cm. with invasion of the musculature.

year ago. Pelvic examination revealed a badly lacerated cervix. Induration was present on the anterior lip. Some erosion and ulceration in the canal. Biopsy proved to be epithelioma of the cervix. Patient was then treated in the usual manner with radium and x-radiation therapy. Her gastro-intestinal history was negative on admission. Patient was seen at regular intervals and as far as the cervical carcinoma was concerned, there was no recurrence after treatment.

On July 31, 1946, during a routine hospital visit, patient stated that for the past 5 weeks she had noticed a mass with some tenderness in the lower mid-abdomen. Had also complained of nausea and vomiting. She had lost weight, but stated that her appetite had

been poor. There was no pain in the epigastrium. No change in her bowel habits, no bloody or tarry stools.

Physical examination revealed a freely movable mass just beneath the umbilicus. This mass was not attached to the uterus and was markedly tender on deep palpation.

Sigmoidoscopic examination was negative for tumefaction. Patient had a gastrointestinal series August 5, 1946. Fluoroscopic examination revealed that the esophagus was normal, the stomach was large, with a constant filling defect on the greater curvature in the body. The cap was normal. The six-hour film showed a small amount of residue. On the 24-hour film, the stomach was empty. Diagnosis of carcinoma of the body of the stomach, moderately advanced, with no evidence of obstruction, was made. Chest roentgenograms were negative.

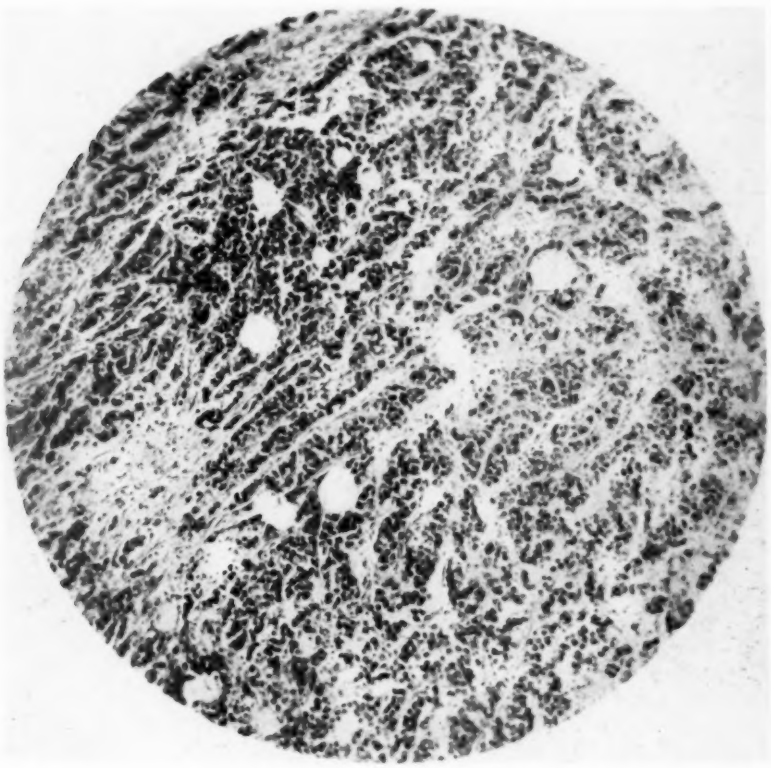

FIG. 8.—Anaplastic carcinoma with marked infiltration of stomach wall.

Patient was admitted to the hospital for gastric resection on August 9, 1946.
Laboratory data:

Hemoglobin 81% (11.6 Gm.)
RBC: 4,280,000
NPN 30; Glucose 107; Albumin 3.26
Globulin 2.23; Chlorides 571 mg.%
Urine negative, except for 1 plus albumin.

Patient was prepared with diet and transfusions in the usual manner and on August 20, 1946, a subtotal gastric resection with a resection of the transverse colon was done.

Findings at operation were as follows: There was no liver metastasis, but there was considerable fixation of the tumor mass involving the lower third of the stomach and transverse portion of the colon. Several nodes were found in the great omentum

Gross. Specimen from the stomach showed the presence of two separate lesions. The larger one measured 10 x 6 cms.[5] The growth was fairly firm in consistency, white in coloration and showed ulceration. The smaller lesion measured 4 x 5 cms.[6] The tumor was soft in consistency and showed papillary projections. Both tumors invaded the muscular coats.

Microscopic. [5 and 6] Both tumors show carcinoma. The tumor cells are anaplastic and show marked infiltration of stomach wall.

FIG. 9.—Anaplastic carcinoma with marked infiltration of stomach wall.

Patient's postoperative course was uneventful until about August 26, when she began to develop signs of obstruction. She was treated symptomatically and on September 10, an exploratory laparotomy was done. A walled-off abscess in the region of the duodenum was found. Drain was inserted.

On September 12, patient suddenly went into coma and ceased breathing. Autopsy revealed congestion and edema of the lungs, peritonitis, cystitis and ulceration of the bladder, adenoma of thyroid and leiomyomatous polyp of cervix.

Conclusion. We have presented three cases of multiple primary carcinomas of the stomach. At no time was it possible clinically, radiologically or gastroscopically to make the preoperative diagnosis as to the multiplicity of the tumefactions.

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INTERNAL HERNIA BEHIND THE JEJUNAL LOOP OF A POSTERIOR GASTRO-ENTEROSTOMY*

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AN UNUSUAL TYPE OF INTERNAL HERNIA was recently encountered on the Surgical Service of the Presbyterian Hospital, and since records of similar cases are rare in the American literature it is being reported in this paper.

CASE REPORT

F. V. Unit Number 644916. *Chief Complaint.* On February 29, 1948, a 48-year-old married German carpenter entered the hospital for the second time complaining of crampy, lower abdominal pain of 24 hours duration.

Previous Admission. He was first admitted to the Presbyterian Hospital approximately 7 years ago for treatment of a stenosing duodenal ulcer. He had suffered from ulcer symptoms for over 12 years and had sustained 2 major complications, the first a gross hematemesis 3 years before admission and the second, a perforation with operative repair 2½ years before admission. His symptoms were those of pyloric obstruction and a gastro-intestinal series revealed 80–90 per cent retention of the motor meal at 6 hours, with a crater in the distal portion of the duodenal bulb. For 3 weeks he was treated conservatively, but at the end of that time he still showed a 50 per cent 6 hour retention of the motor meal by roentgen-ray. In view of this coupled with the past history of both hematemesis and perforation, a partial gastrectomy was done on July 18, 1941. The duodenum was found to be densely adherent to the liver and gallbladder. An ulcer was found on the posterior duodenal wall adherent to and penetrating into the pancreas. About three-fifths of the stomach and part of the first portion of the duodenum including the ulcer were removed. A posterior, retro-colic, Polya type of gastro-enterostomy was done with the afferent limb of the jejunum being approximated to the greater curvature side of the stump of the stomach. The postoperative course was marred by bronchopneumonia followed by empyema which responded to thoracotomy drainage. The gastro-enterostomy functioned well from the start and 5 weeks after the initial operation, he was sent home on a regular diet.

He was followed in the clinic until September 18, 1941, at which time he had no complaints, appeared well and was gaining weight. After this visit, the patient failed to return to the Surgical Follow-up Clinic.

Present Illness. Following the above, the patient was apparently well for the ensuing 7 years until 24 hours before admission when, one hour after breakfast, he noted the onset of severe crampy, knifelike, lower abdominal pain. This was followed by nausea and the vomiting of greenish-yellow fluid. The pain was relieved somewhat by sitting up and was made worse by lying down. During the next 24 hours, he vomited nearly all the food and liquid he attempted to eat or drink. He passed gas by rectum but had had no bowel movement in two days. There was no difficulty with micturition. His pain

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became increasingly severe and he visited his local doctor who gave him Morphine .015 Gm. and Atropine .0006 Gm. by hypodermic and referred him to the Presbyterian Hospital where he arrived 2 hours later.

Physical Examination. Examination revealed an uncomfortable but drowsy male sitting on the edge of the examining table. The pulse was 72, blood pressure 110/60, respirations 16 and temperature 98.0° per rectum. The skin and tongue showed some evidence of dehydration. The heart rate was slow with occasional extrasystoles and bigeminal rhythm. The abdomen showed the scar of the previous operation and was silent. There was marked spasm of both rectus muscles, but this seemed to be largely voluntary and could be relaxed when the patient was distracted. There was some left lower quadrant tenderness and he stated that this was the most uncomfortable area. Rebound tenderness was referred to this area. No mass could be felt. On rectal examination there was some fullness anteriorly above the prostate but there was no definite mass or tenderness.

Laboratory Data. The white blood count was 8,600 with 72 per cent polymorphonuclear leukocytes and 28 per cent lymphocytes. The urine was negative. Four position films of the abdomen showed slight dilatation of the large bowel with gas descending to the level of the upper sigmoid but no gas beyond this point. There was no air under the diaphragm.

Course. The most likely admitting diagnosis appeared to be incomplete large bowel obstruction probably at the level of the sigmoid. Because the picture was definitely clouded by morphia and because neither the vital signs nor the physical findings seemed to indicate immediate operation, it was decided to admit this man to the wards for observation.

After arrival on the ward, the patient was proctoscoped to 18 cm., but no lesion was seen. The proctoscope could not be introduced beyond this point because of spasm. Following the instrumentation the patient vomited 300 cc. of fluid resembling bile.

Subsequently, the patient's symptoms abated somewhat, he dozed a great deal in a semi-sitting position and his physical findings varied. At times the abdomen was quite soft and non-tender. Occasionally the upper quadrants offered more resistance than the lower. He was placed on nothing by mouth, his stomach was lavaged, and he was given an infusion of 1500 cc. of 5 per cent dextrose in saline. Although his signs and symptoms seemed somewhat diminished, his white blood count rose to 14,000 with 86 per cent polymorphonuclear leukocytes 6 hours after admission.

On the following day, the attending doctor found the abdomen soft without distention or tenderness. The patient's complaints now centered on a point somewhat higher and to the left at about the level of the umbilicus. Although he occasionally regurgitated an ounce or so of clear, watery, non-fecal smelling material, intestinal obstruction now seemed less likely. On the other hand, the picture suggested the presence of a penetrating marginal ulcer, so he was allowed milk and amphogel by mouth.

During the day he behaved peculiarly in that he appeared to rest quietly or to doze in a semi-sitting position until examined by any of the staff. Then, as his bed was lowered, he would begin to moan and to complain bitterly of his pain. This suggested a strong functional element in the symptom complex and, indeed, on one occasion he promptly fell asleep after receiving a sterile hypodermic. Drug addiction was also suspected, but his wife denied any knowledge of this nor would the patient himself admit to any. It did not occur to us until later that the change in position incident to the abdominal examination might legitimately augment the symptoms due to the peculiar lesion present.

Laboratory studies this day revealed a white count of 12,900; hematocrit 45.6 per cent; plasma proteins 6.7 per cent; CO_2 29.8 mEq/l; Cl. 101.4 mEq/l; direct Na 137.4 mEq/l; K 4.1 mEq/l; all blood chemistry values being within normal limits. A repeat erect film of the abdomen showed some increase in the gas contained within the large bowel and the findings were again reported as consistent with low grade obstruction of the left colon.

Later that day and during the night the patient's pain became more severe and steady and failed to respond to sedatives, milk or amphogel. A repeat upright film of the abdomen showed the same general appearance as before, but now there appeared, in addition, a fluid level in the stump of the stomach and some moderately dilated loops of small bowel. There was still no air under the diaphragm. He continued to vomit small amounts of clear fluid and the white count rose to 15,600 with 90 per cent polymorphonuclear leukocytes, but the pulse, temperature, respirations and blood pressure remained within normal limits. He died suddenly that night in considerable pain, 81 hours after the onset of his symptoms.

Significant Post Mortem Findings. Autopsy showed a moderately distended abdomen which contained approximately 2000 cc. of blood-tinged fluid. The large bowel was two to three times the normal calibre with gas extending as far as the sigmoid where the

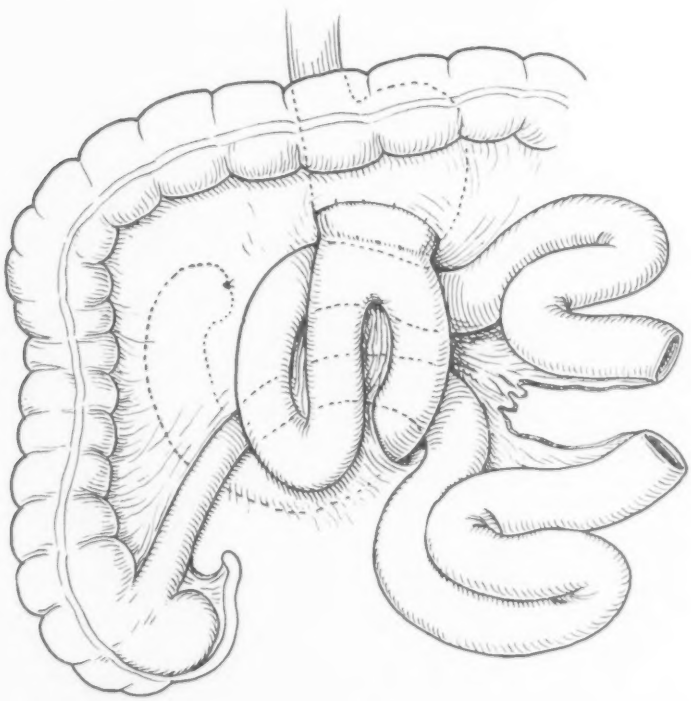

FIG. 1.—Diagrammatic sketch of the internal hernia found at autopsy. The entire small bowel from the mid jejunum to a point 15 cm. from the ileocecal valve had passed behind the jejunal loop of the posterior gastro-enterostomy from right to left. With the transverse colon reflected upward, as pictured, the hernial ring is formed by the afferent jejunal limb anteriorly, the gastro-enterostomy and transverse mesocolon superiorly, the transverse mesocolon posteriorly and the ligament of Treitz inferiorly.

lumen was uniformly constricted without any evidence of an actual organic lesion. The ascending and transverse colon and mesocolon—especially on the right near the hepatic flexure were the site of considerable edema and subserosal hemorrhage. This was found to be due to obstruction of the mesenteric veins. Almost the entire small bowel from mid jejunum to a point about 15 cm. proximal to the ileocecal valve was bluish purple in color with extensive edema and subserosal hemorrhage both in the bowel wall and in

the mesentery. This entire segment of bowel was found to have passed behind the gastro-enterostomy loop from right to left through the space formed (with the transverse colon reflected upward) by the afferent jejunal limb anteriorly, the gastro-enterostomy and the transverse mesocolon superiorly, the transverse mesocolon posteriorly and the ligament of Treitz inferiorly (Fig. 1). Although this bowel segment was occluded at its proximal and distal limits so that this, in effect, constituted a closed loop, the lumen was only slightly distended. The major disturbance seemed to be more one of venous distention and hemorrhage as a result of occlusive stretching and compression of the root of the mesentery at the hernial ring. Here, the superior mesenteric vein was markedly constricted with great engorgement peripheral to this point. Fibrinous adhesions were present between almost all juxtaposed loops of small bowel. The afferent jejunal limb was somewhat stretched, reduced in calibre and blanched. Proximal to the ligament of Treitz, the duodenum was dilated approximately twice normal size.

Microscopic sections through the involved areas showed extreme engorgement of all venous and capillary channels in all layers of the bowel wall. This was most prominent in the mucosa where every villus was swollen with congested capillaries. The submucosa was edematous and its veins were packed with red cells. The muscularis and serosa were similarly edematous and congested but to a lesser extent. There was no evidence of thrombosis or gangrene.

COMMENT

Although there was ample cause for ultimate death in this case, the reason for the sudden exodus is not clear. The extravasation of fluid and the extensive pooling of blood in the mesentery, together with stretching of the latter might possibly have resulted in vascular collapse. Since the heart during life was subject to abnormal rhythms, it is also conceivable that sudden cardiac arrest could have occurred through reflex mechanisms secondary to the above.

This patient should have been operated on shortly after reaching the hospital, or, at the latest, by the time the pain recurred in increased intensity and the white count rose to 15,000. The staff was misled from the start by the fact that the patient arrived at the hospital heavily sedated with morphine. It serves to emphasize once again the danger of employing morphine in the presence of an acute abdomen before the diagnosis has been made.

This case also illustrates a point which has been frequently brought out by others, namely, that in the presence of previous abdominal operations, the appearance of or increase in pain with the assumption of certain bodily positions is a warning sign which must not be ignored. If this is a persistent finding, it almost always indicates an intra-abdominal catastrophe.

DISCUSSION

This interesting complication of posterior gastro-enterostomy was first described by Peterson[1] in 1900, and is sometimes known as Peterson's hernia. In 1934, Himmelman[2] collected 36 cases from the literature, and in 1938, Moiroud, Salmon and Bouillon,[3] mentioned six additional cases apparently not included in Himmelman's series, plus one of their own. Since then, additional cases have been reported by Mayo, Stalker and Miller[4] and by Suiffet[5] making a total of 45 cases at the present writing. In the English

language, four reports may be found[4, 6, 7, 8] in two of which[6, 8] there are excellent illustrations of the abdominal viscera as found at either operation or post mortem.

In the vast majority of cases the presenting problem was one of small intestinal obstruction. In only a few was the principal pathology, as in ours, one of venous occlusion. In not all cases was there an acute incarceration or strangulation of the bowel, some cases presenting the picture of chronic low grade upper intestinal obstruction. In no case was the correct diagnosis made beforehand.

In 1934 Koch[7] gave the mortality for this and other types of internal hernia about a gastro-enterostomy as approximately 50 per cent. Early operative intervention is clearly of paramount importance.

Several authors[2, 3, 4, etc.] have suggested that, as a prophylactic measure, the afferent jejunal limb should be sutured to the transverse mesocolon in all posterior gastro-enterostomies. This measure is practical only if it can be done without angulating the afferent limb in any way that might interfere with its function.

SUMMARY

A case is presented and a brief discussion rendered of internal hernia behind a posterior gastro-enterostomy. With the transverse colon reflected superiorly, the hernial ring is formed anteriorly by the afferent limb of the jejunum, superiorly by the gastro-enterostomy and the transverse mesocolon, posteriorly by the transverse mesocolon and inferiorly by the ligament of Treitz.

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